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TITLE: Lycopene Supplementation in the Complementary Management of PSA Failure: A Randomized Placebo-Controlled Trial for Prostate Cancer Survivors

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INTRODUCTION:

African-Americans record the highest mortality rate for prostate cancer as a result of higher incidence, late detection, and possible more aggressive biological disease variant. Years after successful treatment by surgery or radiation, some patients present with biochemical (PSA) relapse or failure for which the effects of salvage therapies remain unknown. Some studies have reported suppression of carcinogenesis and prolonged disease-free survival by lycopene. This trial targets African-Americans who may benefit from complementary lycopene supplementation given that they have been reported to have significantly lower plasma lycopene in comparison with their white counterparts. A placebo group will not be necessary as we want to compare the cancer inhibitory effect of a single nutrient supplement, Lycopene, and a whole-food (pure tomato-extract) lycopene supplement Lyc-O-Mato® that contains other antioxidants working synergistically to produce additional benefits. The study will recruit 78 men with biochemical failure defined as three consecutive rising PSA after undetectable levels following radical prostatectomy or above the lowest value attained (nadir) following radiation therapy, or at least one PSA test above 0.4ng/ml, randomize them into one of two study-arms for a 12-month intervention, blocking by disease severity on the basis of their Gleason score at diagnosis. Patients will be recruited from urology offices in Nashville including Nashville General Hospital, Vanderbilt University, and Urology Associates, and from the community by media advertisement and direct invitation of men identified through the cancer registry and local prostate cancer support groups. Baseline data will be collected at recruitment after eligibility determination, and informed consent, patients will be monitored for adverse events and compliance weekly in the first month, bi-weekly in the second, and monthly thereafter. A safety monitoring plan is in place to stop the study or withdraw patients in case of serious adverse events. At baseline and the 4 quarterly follow-up time points, blood will be collected to measure free and total PSA, lycopene, the biomarker of oxidative stress isoprostane, and testosterone. Clinical status, QOL score, dietary assessment, and body fat measures will be collected to compare intervention effects. Blood and urine samples will be stored for future analysis of biomarkers of inflammation and DNA damage, and for gene extraction to study their interactions with lycopene in the inhibition of prostate carcinogenesis.

BODY:

Statement of Work:

Task 1: Start-Up Phase: (1-3 months)

This phase was initiated at the study onset but as not completed until much later in August of 2006.

i A post-doctoral fellow, Abu Taher, MBBS., MPH., who is very interested in cancer research, highly motivated, and has shown willingness to work on this study was identified in September 2006, having been hired through another prostate cancer grant.

ii The research assistant that will be assigned to work on this project is Libnir Telusca, MSPH, was identified in July 2006. He currently holds a senior research assistant position in the department of surgery at Meharry Medical College, and he will be able to spend part of his time on this project. Other research staffs identified for this study include:

Meharry Site:

This site will be located at the Clinical Research Center (CRC) at Meharry. Lavenia Crutcher, RN, will be the nurse coordinator in charge of patient management at this site. Ms. Crutcher was identified in October, 2006.

Vanderbilt Site:

This site will be located at the Clinic Research Center at Vanderbilt University Medical Center (VU), and Sandra Motley, RN., MBA will be in charge of patient management at this site. Ms. Motley was identified in July 2006.

iii First meeting between PI, Co-PI and the consultant:

At the inception of this grant the PI had two meetings with the project consultant, Omer Kucuk, M.D., in February of 2006, and it became apparent that he will have to be an investigator on this grant, and this change has been made. In March of 2006 Dr. Kucuk provided two different prostate cancer clinical trial protocols, and expert advice that was utilized by the PI to develop the current protocol for this clinical trial. Each meeting was by telephone, and lasted approximately 30 minutes. The PI contacted Dr. Kucuk as necessary throughout the course of this grant.

The PI held a 1-hour meeting with the Co-PI, Jay H. Fowke, Ph.D., MPH in July 2006, and at this meeting the Co-PI's role, effort, and responsibilities were agreed upon. The Co-PI then went along to identify the study coordinator for that site. At this meeting the PI presented an outline of the specific objectives of this plan and a date for a meeting of all potential collaborators was set for August 2006.

iv First General (Group) meeting at Meharry: August 18, 2006.

All collaborators at the MMC and VU who had contributed to the development of this grant application in 2004/05 were invited to this meeting. Each person received an electronic copy of the funded grant proposal, the statement of work (SOW), and a draft clinical protocol that was developed by the PI over the past six months. This first draft is a product of two revisions based on the comments and input of Dr. Kucuk and Dr. Fowke after they had reviewed the document. Investigators were requested to read this document, not their comments, and be prepared to make contributions for improvement at our next scheduled group meeting. They also received an agenda that indicated that the PI, the Co-PI, and two other members of the team will make presentations at this meeting. (Agenda attached).

Attendance at this meeting was very encouraging as all invited persons were present, and two people who could not come were ably represented.

PI's Presentation: Brief Project Description and Update

The PI started the meeting with a brief welcome, followed by an invitation for self-introduction by all present, followed by the PI's 15-minute presentation that was followed by almost 30 minutes of questions, comments and concerns raised by members. The PI was able to respond to these concerns, and emphasized that the Clinical Trial protocol they received was a first draft, and that changes will be made in line with their expert advice that will be received from the various members. The suggestion that we should exclude a placebo group, and limit the study to a two-arm design was well received as a better option. Members were reassured that they will receive an electronic copy of the 2nd draft of the protocol that will indicate portions to be addressed by each of them. (2nd Draft attached).

Presentation by Dana Marshall, Ph.D.: "Biomarkers of Inflammation"

Dr. Marshall promised to come up with a presentation of possible biomarkers that can be measured in a clinical study such as this one. She described the advantages and disadvantages of some of the biomarkers and suggested that the study use Interleukin 6 (IL-6) a proinflammatory cytokine, as the biomarker of inflammation. Dr. Marshall's laboratory will not be able to measure lycopene at this time, and it was suggested that plans be concluded with an external investigator to do this. The PI indicated that she will contact an interested collaborator, Myron Gross, Ph.D., of the University of Minnesota.

Presentation by Ginger Milne: "Isoprostanes (IsoPs) as Biomarkers of Oxidative stress"

Ms. Milne represented Jason Morrow, M.D., Ph.D., who was unavoidable absent at this meeting, emphasized that that 8-isoprostane-PGF_{2α} (F₂-Isoprostanes) is a very reliable biomarker of oxidative stress, and that this can be measured in their laboratory at VU. (Copy attached)

Saundra Motley then discussed issues such as the development of consent forms, brochures, adverse event record forms, and the importance of designating the clinical trial office. She was particularly concerned about the protocol for randomizing the patients, dispensing of the supplements, follow-up calls, and the creation of a safety monitoring committee. She was willing to develop drafts of the consent forms, adverse event record forms, and to identify other important forms and documented procedures that she had used in previous clinical trials. Some of the main points she raised included:

- Reducing the run-in trial to just one week
- Clearly state that supplement intervention will be for 12 months with 4 quarterly follow-up time-points.
- The need for the PI to assign individual responsibilities and decide on the deadline for members to submit their sections of the proposal.
- Although we had planned to schedule meeting/teleconference that will include Dr. Kucuk, this was not done as all his comments will be included and reported by the PI.

Comments by Anthony Archibong, Ph.D: Measurement of PSA and Testosterone at Meharry.

Dr. Archibong is willing and able to measure PSA (Total & Free) and Testosterone (Total, Free and DHT) in a core laboratory here at Meharry, and will provide detailed information about this. (Copy attached). The PI was indeed very pleased that testosterone can be measured in-house, but pointed out that ToxMed, a commercial laboratory in Nashville, has been measuring her research PSA from 3 years now at a discount cost of \$20 per sample, and it may be better to continue with that laboratory for PSA unless Dr. Archibong's lab can deliver this service at a lower unit cost.

v Copies of 4 clinical trial protocols and the corresponding consent forms that involved supplement intervention, two of which had to do with prostate cancer/lycopene supplements have been reviewed, and they were utilized in the development of the current protocol and consent form for this clinical trial.

<u>Product:</u>	First and Second drafts of the clinical trial protocol. First draft of the consent form. 2 telephone meetings between the PI and the consultant. 1 meeting between the PI and the Co-PI at Vanderbilt. 1 General group meeting. 2 telephone meetings between the PI and Myron Gross, Ph.D. (Collaborator from the University of Minnesota)
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Task 2: Plan Development Outline (4 – 8 months)

i. Data Safety and Monitoring Plan

a) Develop drafts and revise in stages after the input of all investigators:

-A Clinical Trial Proposal:

This proposal will be developed later this year, and will be submitted in response to call for clinical trial proposals by June 2007.

-A Clinical Trial Protocol:

A clinical trial protocol has been developed for this study. This protocol went through 2 stages of development after the change from a 3-arm intervention to a 2-Arm intervention. The new title of the protocol was therefore amended as "Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors".

A biostatistician, Bonnie LaFleur, Ph.D. of Vanderbilt University was approached, and she agreed to become the biostatistician on this grant. Her biosketch is attached. She calculated the appropriate sample size for the study, and developed the statistical methods to evaluate the intervention.

-Consent forms:

Using the consent form developed by Ms. Motley, the PI developed a final draft in line with the format used at Meharry, and this version was submitted to the Meharry IRB in December of 2006 for review. (Copy attached). The consent forms that will be used in VU have been developed by Ms. Sandra with identical content, but designed to meet the VU format. (Copy attached).

-Adverse effect record form:

Ms. Motley provided an adverse event record form for monitoring adverse events, and a flow chart that indicates the procedure for handling any such event that were adapted for this project (Copies attached). The MMC adverse event report form on which all such events are reported to the IRB and the safety monitoring committee will also be used to report such events. (Copy attached).

b) Appoint a medical monitor for this clinical trial

I approached Alphonse Pasipanodya, M.D., in October of 2006. He requested copies of the protocol and description of the role of the medical monitor. After careful consideration of his time commitment he accepted to be the medical monitor for this trial. A copy of his November 2006 support letter is, and a copy of his biosketch are attached. Dr. Pasipanodya is a surgeon in the department of surgery at Meharry.

c) Submit protocol for review by the data safety and monitoring committee at Meharry.

The protocol will be submitted to the data safety and monitoring committee at Meharry after it has been approved by the MMC IRB. A committee for this clinical trial is yet to be constituted. We plan to contact 5 persons, including an independent biostatistician, a bioethicist, an oncologist, and two urologists to make up this committee.

ii Clinical Trial Agent:

-Obtain FDA approval documentation for Lycopene and Lyc-O-Mato

The single nutrient Lycopene supplement, and the Lyc-O-Mato® pure tomato-extract supplements are both nutritional supplements and do not require FDA approval.

-Obtain information about expected adverse effects of this agent if any.

No serious adverse effects are expected from the use of either supplement, and several investigators have reported that the supplement is well tolerated by patients. Clark, P.E. (Urology 67:1257-1261, 2006) did report that one of 36 patients in their trial reported diarrhea (grade 2 toxicity) which the patient thought was related to the supplement. Other toxicities that occurred during this trial were unlikely to be related to lycopene supplements and they included:

- 1 hematuria, hematochezia and lower extremity edema
- 1 patient with long standing history of coronary artery disease recorded anterior ischemia on an electrocardiogram (grade 2)
- 5 transient abnormality of serum glucose
- 1 transient abnormality of serum creatinine
- 1 death after 11 months on the protocol from a previously undiagnosed hepatocellular carcinoma.

iii Outcome Measures:

The outcome measures and the time-points of measurement have been stated on the protocol, and they include primary and secondary clinical and biomarker endpoints. Because of financial constraints and the need to direct our study focus only selected biomarkers will be measured at this time. Blood samples will be stored to measure others in future studies.

-EndPoints (Outcome measures of prostate cancer progression)

Primary Clinical Endpoints:

- a) PSA response to supplementation, defined as a minimum of 50% reduction from baseline PSA maintained for 2 successive readings 3 months apart.
- b) Duration in months of maintenance of PSA reduction from baseline values.

Secondary Clinical End-Points:

- a) QOL response to supplementation, defined as > 25% improvement in QOL scores.
- b) Occurrence and extent of distant metastasis. (X-ray and Bone scan changes)

Primary biomarker endpoints:

- a) Changes in plasma lycopene
- b) Changes in biomarker of oxidative stress: 8-isoprostane-PGF_{2α}

Secondary biomarker endpoints to be measured in future study: (Stored samples)

- a). Changes in DNA oxidation product: 5-OHmdU
- b). Changes in biomarker of inflammation: IL-6

While lycopene is expected to act directly by reducing oxidative stress as measured by isoprostane, it will be useful to also evaluate how lycopene affects other biomarkers that are associated with carcinogenesis, such as DNA oxidation products and measures of inflammation. Blood samples will be stored appropriately to measure both of these secondary endpoints in a future study.

Intermediate biomarker endpoints:

- a). Testosterone: Free, Total and DHT
- b). Plasma IGF-1 and IGFBP-3 (Future study)

Intermediate end-points will be useful in the determination of the mechanism by which lycopene modulates PSA. Male hormones will be assessed in this study, but blood samples will be stored to measure IGF-I and related biomarkers in a future study.

-Response definitions:

Complete PSA response (CR):

- i) Normalization of PSA to undetectable levels for 2 successive determinations a minimum of 3 months apart among patients who had radical prostatectomy.
- ii) Normalization of PSA to nadir value sustained for 2 successive determinations a minimum of 3 months apart among radiotherapy patients.

Partial response (PR):

At least 50% reduction from baseline PSA, short of normalization, sustained for at least 2 successive determinations a minimum of 3 months apart.

Progressive disease (PD):

At least 50% increase from baseline PSA, or the minimum PSA level observed during the study, sustained for two successive determinations a minimum of 3 months apart.

Stable disease (SD):

Does not qualify for CR, PR or PD, with PSA remaining as at the time of randomization, including a less than 50% decrease or increase from baseline levels.

Duration of Response: Duration in months from the first time a complete response or partial response is noticed until the time of disease relapse or progression indicated as a rise in PSA to pre-response level and higher.

Time to Treatment Failure: Duration in months from date of randomization to the date of disease progression, or to the date taken off-treatment due to any reason including toxicity, or to the date of refusal to continue in the study, or to the date of death.

-Data and sample collection time-points/ follow-up have been decided.

Schedule of Study Evaluation:

Laboratory & Other Measures	Data Collection Time Line				
	Baseline Studies	Follow-up Time-Points (Month)			
		3	6	9	12
Clinical Symptom/QOL Assessment	X	X	X	X	X
Body-fat measures	X	X	X	X	X
Dietary Assessment (BLOCK FFQ)	X				X
Three 24-Hour Dietary Recall	X	X	X	X	X
Lycopene & Vitamin E	X	X	X	X	X
8-isoprostane-PGF _{2α}	X	X	X	X	X
Serum PSA (Free & Total)	X	X	X	X	X
Fatty-acids	X		X		X
Testosterone (Free, Total, DHT)	X	X	X	X	X
Comprehensive Metabolic Panel (CMP)	X	X	X	X	X
X-rays and Scans (Abstracted from Medical Record)	X	As clinically available			

-Laboratories/collaborators that will measure biomarkers:

Anthony Archibong, Ph.D. (Associate Professor)

Department of OB/GYN, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd.

Nashville, TN 37208. Tel. 615-327-5714 Fax: 615-327- Email: aachibong@mmc.edu

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-Laboratory analysis plan

Laboratory	Biomarker	Lab. Assay	Sample	Time
Archibong	Testosterone	Solid-phase radioimmunoassay. Kits from Diagnostic Systems Laboratory Inc. Webster, TX. Kit: DSL 4000 / DSL 9600	2.0ml serum	I week
	Testos /DHT			
Morrow	Isoprostane	Gas chromatography	3.0ml plasma	2 week

			1.5ml urine	
Gross	Lycopene	High performance liquid chromatography	2.0ml plasma	3 weeks
ToxMed	PSA	Microparticulate Enzyme Immunoassay (MEIA). Abbott AxSYS system.	2.0ml serum	1 week
Kennedy Krieger	Fatty-Acids	High performance liquid chromatography	2.0ml plasma	3 weeks
To be determined	Vitamin E	High performance liquid chromatography	1.0ml plasma	

iv Statistical analysis:

-The project statistician is Dr. Bonnie LaFluer of the department of biostatistics at VU. She has calculated the required sample size using the PSA slope technique, and has also developed a data analysis plan. An electronic data collection program will be developed to include all study questionnaires, and this program will be utilized for all patient interviews. Information received from laboratories or abstracted from medical records will also be entered into this program. Collected data can be transferred to SPSS or SAS is required. Nutrient intake information obtained from the Block FFQ will be entered directly into the SPSS database. The PI/Investigators can carry out interim data analysis at any time-point. This data analysis performed by the statistician in SAS will be utilized in reporting the study findings. Most of the study data will be collected in real-time, while information that become available weeks after the interview can then be entered at that time.

Comparative analysis of the baseline differences in PSA (total & free), micronutrients (lycopene, fatty-acids, biomarkers (8-isoprostane-PGF_{2α}, Total & Free testosterone, DHT), physical measurements, and micro-nutrient intake estimates from the BLOCK FFQ between men in Study Arm-A and Study Arm-B will be assessed by basic statistical tests such as independent sample t-test. Other characteristics like age at diagnosis, current age, PSA at diagnosis, Gleason score will also be compared by t-test to document comparability of both study arms at baseline. Correlation between the nutrients and the biomarkers will be assessed by Pearson's (skewed data) or Spearman's (normally distributed data) correlation, depending on the pattern of distribution, at baseline.

The effect of the interventions will be analyzed based on evaluable patients as well as by intent-to-treat. This trial is a 2-arm randomized study with the treatment arms being Lycopene capsule vs Lyc-O-Mato ® capsule. The primary biomarker outcome measures are serum PSA (Free & Total) and 8-isoprostane-PGF_{2α}.

Three main methods will be utilized in this analysis:

i) Changes in mean measures of biomarkers

Mean values for biomarkers will be compared across both study arms using Paired-sample t-test to compare the pre- and post-intervention effect of each treatment.

ii) Changes in biomarker slope will be assessed in two ways:

a) Comparing mean slope changes during intervention across study arms for PSA and other biomarkers.

b) Comparing mean changes in slope between pre- and post-intervention PSA measures across study arms. (Multiple PSA measures are usually available for prostate cancer patients)

iii) Proportion of patients with appreciable PSA reduction (or other biomarker changes) will be compared across treatment group by Chi-Square test.

a) Appreciable PSA and other biomarker reduction (or increase) will be set at 30%, 50% and 70%.

b) Proportion comparison for those who had complete, partial, or no PSA response, or disease progression (increased PSA) between Study Arm-A and Study Arm-B will be by Chi-square test. Response in this study has been defined as follows:

-Complete PSA response (CR):

- i) Normalization of PSA to undetectable levels for 2 successive determinations at least 3 months apart among patients who had radical prostatectomy.
- ii) Normalization of PSA to nadir value sustained for 2 successive determinations at least 3 months apart among radiotherapy patients.

-Partial response (PR):

≥50% reduction from baseline PSA sustained for at least 2 successive determinations at least 3 months apart.

-Progressive disease (PD):

≥ 50% increase from baseline PSA, or the minimum PSA level observed during the study, sustained for two successive determinations at least 3 months apart.

-Stable disease (SD):

Does not qualify for CR, PR or PD, with PSA remaining as at the time of randomization.

In addition to these three main methods of analysis, the main effect of lycopene intervention (PSA reduction), and the effect interaction with prostate cancer treatment, (radical prostatectomy or radiation), can be tested. If the interaction effect upon any of the primary endpoints is statistically significant, then a stratified analysis will be necessary, evaluating the effect of lycopene separately for each treatment stratum.

The demographic and food frequency questionnaires will be completed by the R/A. All other information will be collected by the nurse coordinators. Data will be entered into an SPSS database prepared by the PI in consultation with the statistician.

Covariates: Only disease severity by the Gleason score will be controlled for by the study design. Patients will be randomized into study arms within Gleason score strata as indicated below:

Gleason Score < 8

Gleason Score 8-10

All other biomarkers, body fat measures, and lifestyle variables will be controlled for by statistical methods.

- vi. Third meeting between the PI and Omer Kucuk:

A final telephone meeting took place between the PI and Omer Kucuk in November 2006 after a final draft of the protocol had been reviewed by him. Copies of all the other research documents were also sent to him and he confirmed his satisfaction.

- vii. Host two seminars at Meharry Medical College

- a) Omer Kucuk:

Title of presentation: “Lycopene in the etiology and control of prostate cancer progression”.

Date: Monday March 5th at 12:00noon.

- b) Dr. Ram Dasari (Urologist from Urology Associates):

Title of presentation: “PSA Failure after local treatment of prostate cancer: What next?”

Date: Friday February 9th at 12:00 noon

Neither of these seminars has taken place at this time, but they will take place within the first quarter of 2007. The venue will be the Cox Auditorium, 3rd Floor School of dentistry, Meharry Medical College. Invitation will be open to all faculty and students of MMC and VU, and special invitation to the members of this research team.

- viii. Visit to potential recruitment sites:

The PI / Post-doctoral fellow have visited the Vanderbilt Urology clinic in June 2006 and have been introduced to the nurses in that clinic, Ms. Sonya Moore. A system will be put in place to display the study brochures in the waiting room. This aspect will be coordinated by the Co-PI (Jay Fowke) and the nurse coordinator for that site, Ms. Motley.

The PI / Post-doctoral fellow have visited the Urology Associates, and have met with their research manager Rick Trotter. The urologists will be informed about the study, and a strategy will be put in place to remind them to inform eligible patients about the study.

MMC is in the process of hiring Rodney Davis, M.D. to take over the urology practice at Meharry. He is part of this project, and his letter of support is attached.

ix. The IRB application to Meharry was submitted on December 8, 2006. (Copy attached).

Product: IRB Application submitted:

Proposal/Protocol and other documents

Consent forms

Adverse effect record form

Adverse event reporting form

Flow chart procedure for adverse event occurrence

Description of statistical analysis method for the study

List of collaborating laboratories/investigators, and laboratory assay techniques.

Not yet accomplished:

Input from the Meharry data safety and monitoring committee

2 project seminars

Task 3: Feasibility information from study sites (6 – 9 months)

i Urologists and oncologists willing to enroll their patients in this study have been identified as listed above.

ii Investigators from other centers outside Nashville will not be included in this trial.

iii Prostate cancer statistics from TN state cancer registry is available but cannot be made available until the appropriate IRB approvals have been obtained. The annual incidence of prostate cancer among African-American men in TN from 2000 – 2005 averaged 108 cases, ranging from 86-122 cases per year, and a projected 30% of prostate cancer survivors might develop biochemical failure after 15 – 20 years of diagnosis. In a review conducted in 1994, there were 431 men seen at the VUMC with PSA recurrence and 24 (5.5%) were African-American. This number will be slightly higher now that prostate cancer patients seen at Meharry are referred to VUMC, and those from the VA are also managed at VUMC. Currently over 200 patients are diagnosed annually at the VUMC with prostate cancer, of which 10-15 will meet the study eligibility criteria. Statistics from Urology associates has not yet been made available but they are projected to have up to 70% of all prostate cancer patients in this area.

iv. Develop strategic plans to meet clinical trial recruitment goals: See description above.

v. Teleconference with investigators from outside Nashville is no longer applicable.

vi. The draft of clinical trial proposal has not been prepared at this time. This is planned for later on in the year.

vii. A seminar for recruiting Clinical Trial Participants titled “Recruiting Minorities for Prostate Cancer Research with Respect, Beneficence and Justice” addressed strategies for reaching the medically underserved men. This talk was presented by the PI at the 29th Annual Matthew Walker Surgical Symposium & The 58th Annual Hale-McMillan Heritage Lecture, Meharry Medical College, Nashville TN, in May 2005. The PI plans to repeat this presentation at other public forums including African-American gatherings in churches or health fairs.

viii. Recruitment brochure. (Copy attached).

ix. The final draft of study questionnaires have been pilot tested since June 2006.

x. Since we are working directly with the urology clinics we shall not be needing the community outreach core at Meharry and Vanderbilt. However we plan to consult with them and utilize their network system before we start the clinical trial proper.

Community activities:

The PI and Post-doc have attended meetings of the USTOO Nashville Chapter, a prostate cancer support group. There were no African-American members at the meetings we attended, so we decided to start an USTOO Meharry Chapter to attract this group of men. The Chapter is new and has only 5 members at this time. In September of 2006 four of the chapter members attended an USTOO International Prostate Cancer Support Group Training (USTOO University) in Columbia SC. We are aggressively reaching out to our community and will be involved in a national USTOO International prostate cancer awareness, advocacy & action launch on June 15th titled “SNEAKERS @ WORK”. This is one way of providing, hope, education and care to prostate cancer patient, and it may also provide a forum for us to talk about participation in research such as ours.

[US TOO International, 5003 Fairview Ave. Downers Grove IL 60515-5286, is a 501 (c) (3) charitable organization founded in 1990 by and for Prostate Cancer Survivors, their families and men at risk.]

USTOO Nashville:

Chapter facilitator: Judy Thurman Tel 615-329-6367 Email thurms5@yahoo.com
Contact: Yolanda Holmes, RN Tel 615-289-7300
Meeting time: 2nd Tuesday/Month, 7:00 pm
Location: Gladys Stringfield Owen Educational Center, Baptist Hospital

USTOO Meharry:

Chapter facilitator: Flora Ukoli, (PI) Tel 615-327-5653 fukoli@mmc.edu
Chapter Leader: Bert Taylor. Tel 615-406-7379 btaylor13@worldnet.att.net
Chapter coordinator: Charles Gilmore Tel 615-333-6038 cjgil@comcast.net
Meeting time: 1st Thursday of the month, 7:00pm
Location: Department of surgery conference room, Meharry medical college.

American Cancer Society: Man-To-Man prostate cancer support group

Contact: Susan Manning. Tel 615-341-7313 & 615-327-0991

Product: List of cooperating urologists in Nashville
List of prostate cancer support groups, contact person and telephone number
Prostate cancer statistics summary from all study sites
Brochure & questionnaire
1 seminar
2 meetings with urology clinics in Nashville
Outreach and recruitment plan

Task 4. Development of Data and Sample Collection and Analysis Plan (8 – 10 months)

i Letters of support have been received from all investigators and clinicians at each study site, including their biosketch and support status.

ii The RA and both study coordinators have already been trained to recruit, consent, collect data, and to collect, store and ship samples within our ongoing projects at this time. They have obtained the skills, competence and experience for their role.

-Study room has been identified at the Clinical Research Center at Meharry.

-Storage freezer (-80⁰ C) has been identified also.

-An itemized budget will be completed at the submission of the proposal.

iii After input from all investigators, the budget has been prepared. (Copy attached).

iv. Seminar: Monitoring participant safety in clinical trials

We would schedule this seminar closer to the commencement of the clinical trial such that all the information is fresh in the minds of all the investigators and research staff.

v. The clinical trial proposal will be developed after the funding announcement has been released. The major components of the proposal have been developed with input from all of the investigators.

Product:

Letters of support from all investigators and clinicians. (Support letters attached).
Study budget including subcontracts from other institutions
Training manual for RA and Clinical Trial coordinator
Clinical trial address and contact information for each study site

Task 5: Clinical Trial Proposal (11 – 12 months)

The major components of the grant proposal have been developed, and once the funding announcement is released the grant proposal package will be ready within a two-month period. .

Product:

Clinical trial protocol. (Copy attached).

KEY RESEARCH ACCOMPLISHMENTS: *Bulleted list of key research accomplishments emanating from this research.*

1. A strong multidisciplinary team of investigators, experts, and urologists has been put in place.
2. Five main laboratories have been identified and ready to measure the various study biomarkers.
3. A clinical trial protocol has been developed with input from the various experts.
4. Several other human subject protection documents for the study including study brochure, consent form, HIPAA form, adverse event record form, and the adverse event procedure flow-chart, have been developed.
5. Other study documents such as demographic questionnaire, laboratory report form, 24-hour dietary recall questionnaire have also been developed.
6. The BLOCK FFQ has been selected as the tool to assess dietary history.
7. The FACT-P has been selected as the tool to assess quality of life of the patients (QOL).
8. An IRB application has been submitted to the Meharry IRB. Response is expected.
9. An IRB application package has been prepared to be submitted along with the MMC IRB approval letter.
10. Very cordial relationship has been established with the TN State Cancer Registry, and an IRB application will be submitted and processed once this clinical trial is funded.
11. Two guest speakers, Ram Dasari, M.D., and Omer Kucuk, M.D. are scheduled to present at our seminar on February 9, 2007 and March 5, 2007. (Schedule attached)
12. A prostate cancer support group, USTOO Meharry , a chapter of USTOO International, has been established at Meharry to provide prostate cancer awareness, information, support and care to men, particularly African-American and other medically underserved persons living with prostate cancer.
13. Maintained networking partnership with 6 communities/churches in Nashville.
14. Urologists from an additional institution, Urology Associates, Nashville, have agreed to allow access to their patients as potential participants. .

REPORTABLE OUTCOMES: *Provide a list of reportable outcomes that have resulted from this research to include:*

Presentations:

August 18, 2006. The role of lycopene in biochemical failure among prostate cancer survivors.

CONCLUSION: *Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.*

The study has now met its goal to develop a clinical trial protocol to evaluate the role of lycopene in the control of biochemical (PSA) failure and to submit an IRB application to conduct the study if approval is granted. The consent form, HIPAA form, study questionnaires, and other relevant documents have been developed for this study in collaboration with experts from across the U.S. Laboratory scientists have now joined the group, and will be able to measure the various biomarkers in their laboratories.

The study has arranged to have access to at least 80% of prostate cancer survivors presenting at their urologists office with biochemical failure, and the others we plan to access through the mass media. With our strong and growing community network we anticipate encouraging response to this study and we predict meeting our participant accrual goals on schedule.

REFERENCES: List all references pertinent to the report using a standard journal format (i.e. format used in *Science*, *Military Medicine*, etc.).

APPENDICES:

1. General Meeting agenda:
2. 2nd Draft of Protocol (3-Arm study): Input requested of various investigators.
“LYCOPENE SUPPLEMENTATION IN THE COMPLEMENTARY MANAGEMENT OF PSA FAILURE: A RANDOMIZED PLACEBO-CONTROLLED TRIAL FOR PROSTATE CANCER SURVIVORS”
3. Laboratory summaries:
 - i) Jason Morrow’s lab: “Isoprostanes (IsoPs) as Biomarkers of Oxidative stress”.
Presentation by Ms. Milne
 - ii) Anthony Archibong’s lab: “Laboratory methods for measuring hormones secreted by the prostate gland”. Submitted by Dr. Archibong
 - iii) Dana Marshall’s lab: “Measures of biomarkers of inflammation”. Submitted by Dr. Marshall
4. Consent form for MMC
5. Consent form for VU
6. Adverse Events Forms:
 - i) Adverse event record form
 - ii) Adverse event procedure Flow-chart
 - iii) MMC adverse event report form
7. Medical monitor: Alphonse Pasipanodya, M.D. of Meharry Medical College.
Biosketch and Support letter
8. IRB application:
 - i) MMC IRB application (13-pg)
 - ii) MMC IRB review comments
9. Study Brochure
10. Proposal Budget and Budget justification
11. Letters of support and Biosketch
 - i) Letters of support of investigators
Ronald Davis
Anthony Archibong
Emeka Ikpeazu
Derrick Beech
Jay Fowke
Bonnie LaFleur
Jason Morrow
Michael Cookson
Myron Gross
Omer Kucuk
 - ii) Biosketch of investigators
 - iii) Biosketch of Nurse-Coordinators

Lavenia Crutcher
Saundra Motley
12. Protocol Final Draft: (2-Arm study with appropriate revised title.)
“Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors”
13. Seminar schedule
14. “The role of lycopene in biochemical failure among prostate cancer survivors.” Presentation by Flora A. M. Ukoli.

Appendix 1.

Department of Defenses (DOD) Clinical Trial Development Award

Lycopene & Prostate Cancer Survival Trial at Meharry

General Meeting:

August 18, 2006

Agenda

- 2:00pm. Welcome by Dr. Flora Ukoli
Self-Introduction of project members
- 2:10pm. Brief Description and Update Dr. Flora Ukoli, (Project PI)
- 2:20pm. Introductory Comments by Dr. Jay Fowke, Co-PI, Vanderbilt University
- 2:25pm. Presentation by Dr. Dana Marshall
(Biomarkers of Inflammation)
- 2:30pm. Presentation by Ginger Milne
(Biomarkers of Oxidative Stress)
- 2:35pm. Participants recruitment issues, Consent forms etc.
Comments by Saundra Motley
- 2:40pm. Comments from other members
- 2:50pm. General discussion & strategic plan: protocol development& submission
- 3:00pm. Close , date for next meeting

Appendix 2. 2nd Draft of Protocol (3-Arm Study): Input requested from various investigators.

Revised August 17, 2006.

LYCOPENE SUPPLEMENTATION IN THE COMPLEMENTARY MANAGEMENT OF PSA FAILURE: A RANDOMIZED
PLACEBO-CONTROLLED TRIAL FOR PROSTATE CANCER SURVIVORS

Principal Investigator

Flora A. M. Ukoli, MBBS., MPH.

**Department of Surgery
Meharry Medical College
Nashville, TN.**

Co-Investigators

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Dana Marshall, Ph.D.

Emeka Ikpeazu, M.D., Ph.D.

Ronald Davis, M.D.

Derrick Beech, M.D.

Vanderbilt University Medical College

Jay H. Fowke, Ph.D.

Jason Morrow, M.D.

Michael Cookson, M.D.

Wayne State University, Detroit, MI.

Omer Kucuk, M.D.

Collaborating Institutions

Vanderbilt University Medical College
Nashville, TN.

Barbara Ann Karmanos Cancer Institute
Wayne State University
Detroit, MI.

FAST FACTS

I. TITLE

Lycopene supplementation in the complementary management of PSA failure: A randomized placebo-controlled trial for prostate cancer survivors.

II. OBJECTIVES

1. Evaluate the feasibility and adherence to lycopene supplementation among African-American men with biochemical failure following prostate cancer treatment.
2. Determine if lycopene or tomato-extract supplements will better impact plasma lycopene.
3. Assess if lycopene and/or tomato extract will decrease serum PSA in treated prostate cancer patients presenting with biochemical failure.
4. Assess the modulation of biomarkers of oxidative stress (isoprostane), inflammation (IL-6), and cell growth by lycopene.

III. PATIENT ELIGIBILITY

1. Ethnicity: African-American.
2. Diagnosis: Histologically confirmed prostate cancer, treated by radical prostatectomy or radiation, seed implantation or external beam radiation.
3. Presentation: Biochemical or PSA failure or relapse.
PSA failure is defined according to treatment received:
 - Men who had radical prostatectomy:
Two successive readings, at least one month apart, of PSA \geq 0.4 ng/ml, after initial fall to undetectable level.
 - Men who had radiation treatment:
Two successive readings, at least one month apart, of PSA above the lowest value attained (nadir) after radiation.
4. Consent: Must sign informed consent to participate in the study.
5. Exclusion criteria:
 - i) Enrolled in diet related trial with overlapping intervention/follow-up period.
 - ii) Taking supplements that are known to contain lycopene, or any micronutrient supplements other than multivitamins.
 - iii) Life-expectancy less than 1 year by clinician recommendation.
 - iv) Mental incompetence
 - v) Erratic life-style, have 5 or more alcoholic drinks/day
 - vi) Extensive travel or institutionalized and cannot keep follow-up appointment.
 - vii) Organ function restrictions.
 - viii) Chemotherapy within 4 weeks of starting intervention
 - ix) Hormonal therapy within 4 weeks of starting the intervention.
 - x) Eligible for a higher priority study.

IV. TREATMENT PLAN

Arm A1: Lycomato Supplement:

Participants in this group will take Lyc-O-Mato (pure tomato extract) dietary supplement that contains 30mgs lycopene on alternate days while also eating their usual diet. Alternate day dosing will continue for 4 weeks to ensure tolerance before increasing to a daily dose of Lycomato.

Arm A2: Lycopene Supplement:

Participants in this group will receive 30mgs lycopene supplement on alternate days while also eating their usual diet. Alternate day dosing will continue for 4 weeks to ensure tolerance before increasing to a daily dose of Lycopene.

Arm B: Placebo / Usual Care:

Participants in this group will receive a placebo tablet (cellulose matrix identical to lycomato supplement) on alternate days for the first 4 weeks before converting to a daily regimen, maintaining a similar pattern with those in the intervention group. They will also continue to eat their usual diet.

V. DURATION OF INTERVENTION

Six months.

VI. ANTICIPATED TOXICITIES

None.

VII. ANTICIPATED ACCRUAL

60 patients over a period of 2 years.

VIII. EVALUATIONS

Clinical symptom assessment, Body-fat measures, CBC with differentials, SMA-12, and electrolytes: At baseline, month-6, and month-12.

Dietary assessment (FFQ), and X-ray / Scan: At baseline, and month-12.

Lycopene, PSA (total and Free), Isoprostane, IL-6, 5-OHmdU & factor NF-B: At baseline, month-3, month-6, month-9, and month-12.

Testosterone Total and DHT), Tocopherol, Fatty-acids, IGF-1, and IGFBP-3: At base-line, month-6, and month-12.

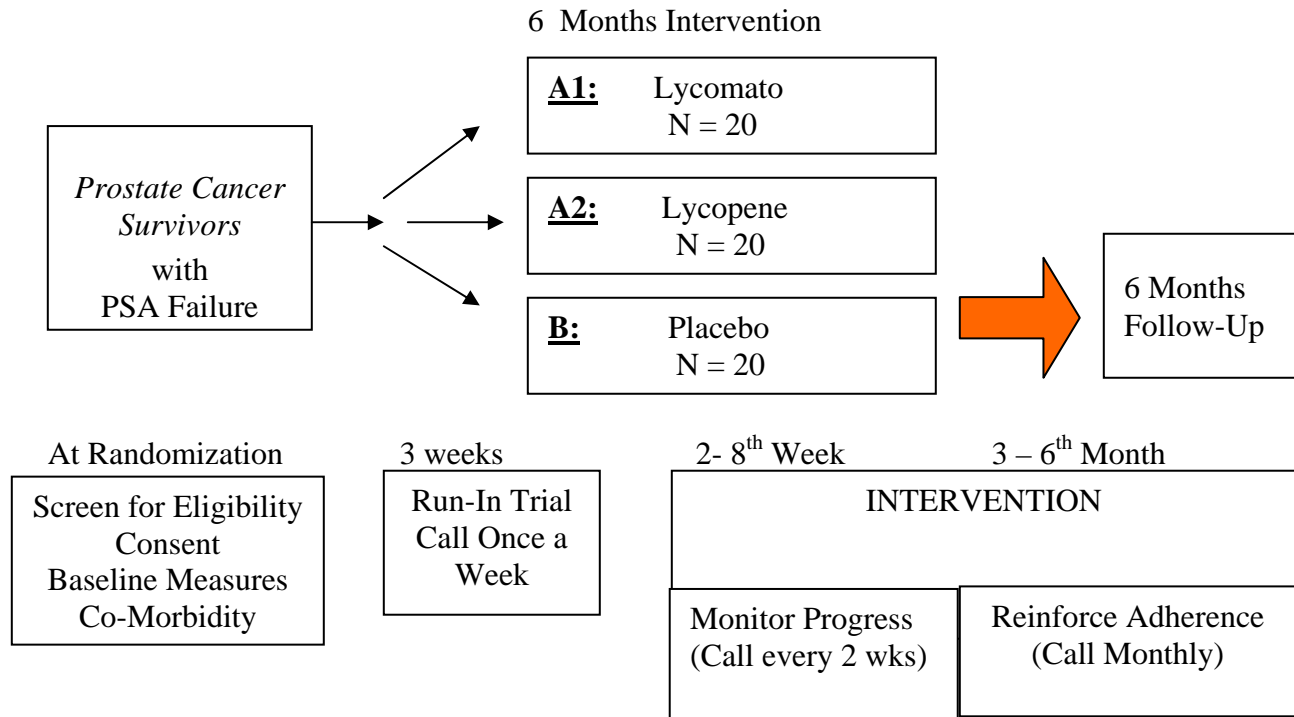
IX. PRINCIPAL INVESTIGATOR : Flora A. M. Ukoli, MBBS., DPH, MPH.

**LYCOPENE SUPPLEMENTATION IN THE COMPLEMENTARY MANAGEMENT OF
PSA FAILURE: A RANDOMIZED PLACEBO-CONTROLLED TRIAL FOR PROSTATE
CANCER SURVIVORS**

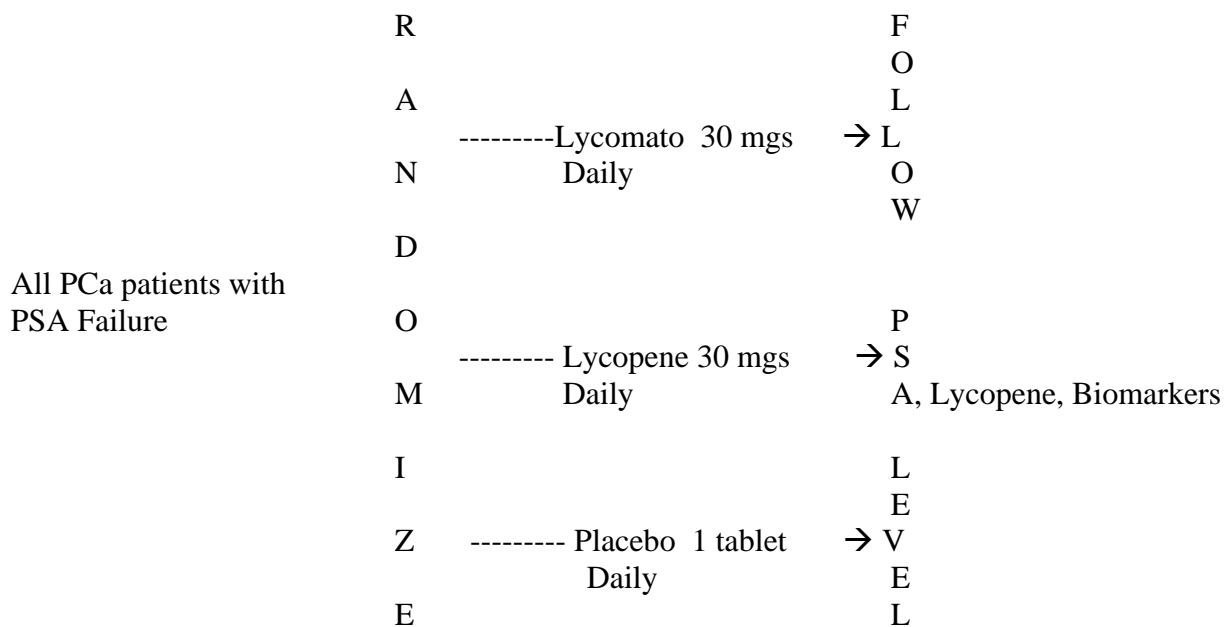
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LYCOPENE SUPPLEMENTATION IN THE COMPLEMENTARY MANAGEMENT OF PSA FAILURE: A RANDOMIZED PLACEBO-CONTROLLED TRIAL FOR PROSTATE CANCER SURVIVORS

Randomization Plan:



SCHEMA



Data Collection Plan

Laboratory & Other Measures	Data Collection Time Line				
	Baseline Studies	Follow-up Studies:			
		Month-3	Month-6	Month-9	Month-12
Clinical Symptom Assessment	X		X		X
Body-fat measures	X		X		X
Dietary Assessment (FFQ)	X				X
Lycopene	X	X	X	X	X
Isoprostane & IL-6	X	X	X	X	X
5-OHmdU & factor NF-B *	X	X	X	X	X
Serum PSA level	X	X	X	X	X
Tocopherols, fatty-acids	X		X		X
Testosterone (total and DHT)	X		X		X
Plasma IGF-1 and IGFBP-3	X		X		X
CBC with differential SMA-12, electrolytes	X		X		X
X-rays and Scans	X	Repeat as clinically indicated			X

*Additional biomarkers of oxidative stress in peripheral blood lymphocytes include:

1. DNA oxidation products 5-OHmdU Oxidative DNA damage (ODD)
2. Oxidative stress induced nuclear transcription factor NF-B

(Ginger / Dana to Modify): Please advise on measures of oxidative stress, DNA oxidative damage and things like that because I have no scientific knowledge in that direction!)

Target Accrual:

60 patients (20 patients in each of the 3 study arms)

Accrual Period:

2 years

1.0 OBJECTIVES

- 1.1 Evaluate the feasibility and adherence to lycopene supplementation among Africa-American men with biochemical failure following prostate cancer treatment.
- 1.2 Determine if lycopene or tomato-extract supplements will better impact plasma lycopene.
- 1.3 Assess if lycopene and/or tomato extract will decrease serum PSA in treated prostate cancer patients presenting with biochemical failure.
- 1.4 Assess the modulation of biomarkers of oxidative stress (isoprostane), inflammation (IL-6), and cell growth by lycopene.

2.0 BACKGROUND

2.1 Prostate Cancer Epidemiology:

Cancer of the prostate is the most commonly diagnosed solid malignancy and the second leading cause of cancer-related death in men living in developed countries (1). African American men have the highest incidence of prostate cancer in the world, and mortality among African-Americans is approximately 2-fold higher than in whites (1-3). Although familial aggregation (4,5) is important in cancer epidemiology, only 10% of prostate cancers are due to the familial type. The prevalence for prostate cancer continues to rise among all ethnic groups in America as prostate

cancer screening using digital rectal examination (DRE) and the prostate specific antigen (PSA) blood test become more widely available (6). Up to 185,000 prostatectomies were performed in 2001, about 70% among men 65 years and older (7). In 1999 The National Cancer Institute (NCI) estimated that 17% of the 9.6 million cancer survivors in the United States had been diagnosed with prostate cancer, giving an estimated number of 88888 prostate cancer survivors (8). Report from the SEER program states that 233,520 prostate cancers were recorded between 1975-1997 of which 10.9% were African Americans. Among Non-Hispanic white men the proportion with localized / regional disease increased from 73.8% to 80.4% in 1975-1987 and 1988-1997. The equivalent rates were 65.5% and 74.5% among African American men (9). Between 1986 and 1991 there was a dramatic increase in the number of men diagnosed with prostate cancer in the United States (10), and this has led to a decrease in the proportion of men diagnosed with pathologically advanced disease (11). Overall survival, recurrence-free survival and quality of life outcomes vary with treatment options which in turn depend on patient selection criteria (12-15). Quality of life outcomes such as sexual dysfunction and urinary incontinence are more common among men who had radical prostatectomy while men who had radiotherapy have worse bowel function and urinary distress from irritative voiding symptoms (16,17). With improved screening and early detection of prostate cancer in younger men new approaches in addition to primary treatment by surgery or radiation are needed to meet the clinical needs of the growing population of survivors with PSA recurrence (18-21).

2.2 Dietary Risks of Prostate Carcinogenesis:

Incidence of prostate cancer differs greatly in countries all over the world, the American black records the highest rate while the Asians have the lowest. Autopsy studies show that the rate for latent prostate carcinomas is similar for both high and low incidence regions. Differences are observed when comparing foci size and growth types. In low-incidence countries the foci of latent prostate carcinoma are small with slight proliferating tendency, whereas in high incidence countries the foci are larger and more aggressive. Disparity in the incidence of prostate cancer relates more to differences in cancer promoting and malignant transformation factors such as environmental and dietary factors, rather than differences in cancer initiation factors (22). Epidemiological evidence indicates that dietary fat, by way of altered hormonal action, is a risk factor for prostate cancer development (23). Ecologic and migrant studies over the past decades demonstrate the correlation between greater dietary fat intake and higher mortality of various cancers, including prostate cancer (24). Although saturated fat was observed to have a causal role for prostate cancer in a population-based case-control study among blacks (very high risk), whites (high risk), and Asian-Americans (low risk), other factors were reported to be largely responsible for interethnic risk differences in this study (25). High consumption red meat and fat from animal sources increased risk for advanced prostate cancer among American men but most especially among African Americans (26,27). One of the major nutrients associated with increased risk for prostate cancer are fatty acids. In a prospective cohort study conducted in over 47,000 US men intake of alpha-linolenic (ALA; 18:3n-3) appeared to increase the risk for advanced prostate cancer while eicosapentaenoic (EPA; 20:5n-3) and docosahexaenoic (DHA; 22:6n-3) may reduce the risk of total and advanced prostate cancer. High consumption of fish lowered the risk for prostate cancer, especially for metastatic cancer and this may be the effect of marine fatty acids alone or other factors in fish (27,28). While specific nutrients have been linked to prostate cancer risk, body fat per se and various aspects of body size are also related to the risk of prostate cancer (29). In the same vein, factors that ameliorate obesity, such as physical activity have been shown to be protective against some cancers such as breast, colon and prostate working through its effect on immune function, transit time of digestion,

hormones, and body fat (30).

Epidemiological studies and international trends support the fact that prostate cancer incidence and mortality rates are adversely affected by dietary animal fat and specific fatty acids. Dietary patterns as a whole should be considered as certain nutrient components like monounsaturated fatty acids (MUFA) can derive from both vegetable and animal sources, and only high consumption of MUFA-rich vegetable oils was protective of prostate cancer. The diet rich in vegetable oil MUFA was also high in lycopene, vitamin E, selenium and n-3 fish oils (31).

2.3 Diet May Inhibit Prostate Carcinogenesis:

A host of micronutrients antioxidants, including carotenoids, retinoids, polyphenols, selenium, vitamin E and C, and also vitamin D and calcium have been reported to be protective against prostate cancer. Their effects are significant and complex and affect prostate cancer cell proliferation, differentiation and signaling related to cancer initiation, progression and regression (32). Low plasma levels of antioxidant vitamins are associated with an increased risk of subsequent cancer mortality especially in men above age 60 years and this association site-specific (33). Prospective studies have shown consistently that antioxidants like vitamin E, lycopene, and selenium are protective for prostate cancer (34). In a nested case-control study in Washington county, MD, no significant associations were observed with beta-carotene, lycopene, or tocopherol, but the data suggested an inverse relationship between serum retinol and risk of prostate cancer (35). Findings from a case-control study also supports a protective role for antioxidants like lycopene and beta-carotene especially in younger men and those without a strong familial or hereditary disease component (36). On the basis of their findings from a population-based case-control study that examined the role of foods and nutrients in prostate cancer risk it was suggested that diets rich in olive oil, tomatoes and allium vegetables might reduce the risk of prostate cancer (37). The importance of the effect of environmental and dietary factors is underscored by the increased prostate cancer rate among Asian migrants in America when compared to the very low incidence among their peers in their home country (38). Manipulating diet and thus changing the antioxidant milieu may therefore play a role in reversing or retarding disease progression. Laboratory studies have since demonstrated the effective role of antioxidants in slowing down prostate carcinogenesis (39).

2.4 Biochemical Recurrence (PSA Failure): **(JAY PLEASE IMPROVE)**

Survival following radical prostatectomy, though similar for institutions, depends on technique and experience. The recurrence-free survival rate after radical prostatectomy at the 5-, 10- and 15-years time-points is 84%, 72% and 61% (18). However measurable blood PSA levels may return among many patients, signaling biochemical failure of treatment. This can occur even in the absence of overt signs of disease progression or metastasis. Biochemical failure is clinically defined as three consecutive rising PSA after undetectable levels following radical prostatectomy or above the lowest value attained (nadir) following radiation therapy, or at least one PSA test above 0.4ng/ml (40,41). Age is an independent predictor of biochemical failure but race is not. Pretreatment PSA and Gleason score were also significant predictors of PSA relapse-free survival in multivariate analysis. There was no significant difference between the 5-year PSA relapse-free survival for African-Americans (84.0%) and the matched cohort of White Americans (81.2%) ($p = 0.384$). Race did not predict 5-year PSA relapse-free survival among patients treated with or without NAAD and within low-, intermediate-, and high-risk groups (42). Younger men under 50 years had a lower rate of extraprostatic extension (25% versus 36%; $P < 0.001$), seminal vesicle involvement (2% versus 10%; $P < 0.001$), and positive surgical margins (3% versus 9%; $P < 0.001$) and a greater organ-confined disease rate (65% versus 36%; $P < 0.0001$) than the older men, thus demonstrating greater long-term cancer control (43).

The multivariate time-to-failure analysis using the Cox proportional hazards model for clinical parameters showed the pretreatment PSA level ($p < 0.001$) and biopsy Gleason score ($p < 0.001$) to be the only independent predictors of biochemical relapse among men treated with radiotherapy (44,45). The 5-year biochemical progression-free survival for patients with a Gleason score 8-10 was 65%, 30%, and 20% for patients treated with surgery plus postoperative radiotherapy, radiotherapy alone, and surgery alone. The independent prognosticators for biochemical failure included serum PSA > 20 ng/mL and seminal vesicle invasion; only seminal vesicle invasion was prognostic for clinical failure (46). Another study reported a 5- and 10-year disease-free survival (clinical and PSA) of 67% and 53% respectively, with 19% PSA recurrence rate (47). The 5-year risk of progression for tumors with Gleason score 3+4 and 4+3 was 15% and 40% respectively, $p < 0.0001$ (48). Treatment option, tumor grade of Gleason score 7-10, PSA > 20 ng/ml, higher clinical stage and age at diagnosis are all important predictors of biochemical failure either in the short or long-term. Since initial treatment option is influenced by age, health status, presence of comorbidity, tumor grade and disease stage, radical prostatectomy is the choice for younger and healthier men. The risk of biochemical failure is therefore higher for men diagnosed at a younger age with higher tumor grade and stage at diagnosis (43-49). Overall survival after PSA-detected recurrence following conformal radiation therapy was 58% at five years while cause specific survival was 73% (50).

The treatment option for biochemical recurrence of prostate cancer includes androgen deprivation, cryotherapy, and salvage radiation or salvage prostatectomy, depending on the initial treatment option, the impact of which remains unknown. The median interval from PSA recurrence to cancer death ranges from 5 – 12 years, depending on the cancer Gleason score. The actuarial metastasis-free survival was 82% (95% CI, 76%-88%) at 15 years after surgery and 15% developed biochemical PSA failure and 34% developed metastatic disease within the study period. The median actuarial time to metastases was 8 years from the time of PSA level elevation (40,51). Salvage prostatectomy provided excellent control of radio-recurrent cancer confined to the prostate or immediate periprostatic tissue if performed before the preoperative PSA level rose above 20 ng./ml. After 5 years, 82% had no progression (52). With external beam radiotherapy, extended follow-up demonstrated a decrease in cause specific survival at 15 and 20 years of 64.5% and 37.7% respectively, having all patients dying of unknown causes censored. Of the patients who survived 47% were on hormonal therapy (53).

Hormonal manipulation using anti-oestrogens in breast carcinogenesis or anti-androgens in prostate carcinogenesis are proven methods of chemoprevention of cancer. Other chemopreventive agents such as antioxidants can prevent, delay onset or delay progression of cancer or reverse carcinogenesis. It is therefore important to investigate interventions that will impact this wide range in survival. Diet derived antioxidants are being investigated as chemopreventive agents of prostate cancer. (54). Similarly dietary antioxidants may be useful complements in the management of biochemical recurrence of prostate cancer and researchers have suggested that whole-food tomato intervention rather than the use of single nutrient supplementation may have the potential to halt or retard cancer progression in humans (55) as in laboratory animals (56).

2.5 Hormone Therapy and Prostate Cancer: (EMEKA IKPEAZU IMPROVE)

Androgen ablation using drugs or surgery produces castrate levels of testosterone that inhibits the growth of prostate cancer cells. This therapy can be used in several ways including neoadjuvant, adjuvant and intermittent therapy. Androgen ablation can be achieved by bilateral orchidectomy or administration of estrogens, LH-RH analogs, antiandrogens and progestational agents. Previously only patients with advanced, metastatic or recurrent prostate cancer received

androgen ablation for a median of 3 years or until death. Presently recurrence is diagnosed on the basis of PSA failure and the median life expectancy for such patients is 10-15 years. Consideration to minimize side effects and protect quality of life is therefore very relevant. Thus androgen ablation for these patients must consider the timing (early vs. late), treatment schedule (intermittent vs. continuous) and androgen blockage (total vs. partial). Androgen ablation remains an effective treatment for advanced prostate cancer but there is need to find ways of averting the development of hormone-refractory prostate cancer (57).

In the effort to avoid recurrence among high-risk prostate cancer cases, combined modality treatment using hormonal therapy with brachytherapy and external beam radiation, has been utilized. Five-year PSA recurrence was avoided in 76% of those with Gleason score 8-10 in comparison with 97% in men with Gleason score less than 6. (58).

2.6 Lycopene and Prostate Cancer

Evidence from animal models or cultured cancer cells demonstrate that lycopene and other carotenoids inhibit prostate carcinogenesis. While the mechanism of its action remains under investigation, lycopene is one of the most potent carotenoids by the ability to trap singlet oxygen. Additionally, lycopene administration inhibited human cancer cell growth through a growth factor receptor signaling mechanism (59). Lycopene has been reported to arrest the cell cycle by the induction of apoptosis in LNCaP human prostate cancer cells (60-61). When the MatLyLu Dunning prostate cancer model was treated with lycopene and/or vitamin E for a period of 4 weeks, there was significant development of necrosis within the tumors. While vitamin E reduced androgen signaling lycopene affected testosterone activation by down regulating 5-alpha-reductase and also down regulated prostatic IGF-I and IL-6 (62). Lycopene has been found to act via several pathways such as prostatic IGF-signaling, IL-6 expression and androgen signaling. These mechanisms of action are potentially synergistic in reducing normal and cancerous cell proliferation, reducing DNA damage and improving oxidative stress defense (63). In vivo studies using lacZ mice involved feeding them with lycopene-rich tomato oleoresin (LTO) and inducing them with prostate cancer using two different chemical mutagens. The results from this study showed that the antimutagenic effect of lycopene may be organ specific and prostate cancer was one of the sites susceptible to the protective effect of lycopene (64). However, some animal research reported that lycopene did not have a chemopreventive effect for prostate cancer (65).

Investigators working with prostate cancer cell-lines have also reported the potential synergistic action of various carotenoids present in foodstuffs in the prevention of prostate cancer in humans. The effects of 15 kinds of carotenoids on the viability of three lines of human prostate cancer cells, PC-3, DU 145 and LNCaP, were evaluated and they significantly reduced prostate cancer cell viability (66). Strong inhibitory effect of prostate carcinoma cell proliferation was also observed for lycopene and alpha-tocopherol that was synergistic and this effect was not shared by beta-tocopherol, ascorbic acid and probucol (67). Animal studies tend to support the inhibitory effect of lycopene on spontaneous prostate cancer mutagenesis (68). Administration of antioxidants (vitamin E, selenium and lycopene) to the 12-T-10 Lady transgenic mice model resulted in a 4-fold reduction in the incidence of prostate cancer in comparison with the untreated mice both in mice on standard and high fat diets. Anti-oxidant related toxicity was not reported showing that the diet supplemented by antioxidant was well tolerated (69). Some studies failed to find this protective effect of lycopene in laboratory rats (65). Since lycopene has been found to inhibit the growth of normal human prostate epithelial cells in vitro it may also be useful in controlling prostate tissue development and enlargement in vivo. This is particular important in the management of benign prostate hyperplasia, a potential precursor of prostate cancer (70), forming the basis of several

lycopene and prostate cancer studies in human populations.

Lycopene exists in foods more in the all-trans isomer (80-90%) while the opposite is true of plasma and benign or malignant prostate tissue where 60-70% and 80-90% respectively exists in the cis-form. Other carotenoids are present in the prostate as well (71). A few case-control studies have reported the lack of protective effect of lycopene for prostate cancer in the US (72) and from Hawaii (73). Several investigators have reported convincing findings that greater lycopene intake from tomato-based foods is associated with reduced prostate cancer risk (33-37). Recommendations to increase consumption of vegetables and fruits to reduce cancer risk and tomato-based foods especially for prostate cancer risk reduction were based on such convincing data (74). This protective association of lycopene was reported to be weak in some case-control studies (75). Several of these case-control studies conducted dietary assessment by questionnaires, measured plasma levels of carotenoids and the odds ratio (OR) was used to measure the strength of association with prostate cancer risk. Bivariate and multivariate logistic regression models were used to estimate OR for individual nutrients, controlling for some or all of age, race, years of education, family history of prostate cancer, pack-years of smoking, alcohol consumption and daily caloric intake. Lycopene usually was reported as one of the protective nutrients (76). The Health Professionals Follow-up Study (HPFS) recruited 47,365 participants and their investigations of the diet confirmed that frequent consumption of tomato products was a protective factor for prostate cancer even after controlling for the consumption of fruits, vegetables and olive oil. They compared men who reported eating two servings/week to those who ate one serving/month and observed a RR of 0.77, CI 0.66 – 0.90 (77). High intake of lycopene in tomato products and other lycopene-containing foods reduced risk of prostate cancer and might also reduce the progression of prostate cancer (78). Other large cohort studies from the Netherlands (79), the UK (80), and the United States (81) however reported no association between lycopene and prostate cancer. In a nested case-control study Huang et. al. examined prostate cancer risk using prediagnostic blood levels of antioxidants from samples collected between seven and twenty-two years prior to diagnosis, and found an inverse relationship between gamma-tocopherol and prostate cancer risk, but not for lycopene (72). Several review articles have reported findings from both case-control and cohort studies that investigated the role of dietary lycopene in prostate cancer risk. Some studies measured lycopene levels in the blood while others estimated dietary intake of lycopene using food frequency questionnaires. It is problematic to compare findings across such studies because of variability in the ability of such tools to measure low levels of tomato-food consumption. Also variations in food preparation methods may alter the bioavailability of lycopene across these nations. Reviewers are in agreement that lycopene, among other micronutrients, is a promising antioxidant in the control of prostate cancer (82-86). Prospective cohort studies are also consistent that selenium, vitamin E, pulses and tomato/lycopene have a possible protective role against prostate cancer (19). Even in a low incidence region like China, prostate cancer risk declined with increased consumption of lycopene and other carotenoids and a dose-response relationship was demonstrated (87).

Few studies have had the opportunity to look at the prostate cancer - lycopene associations among African-Americans. The Third National Health and Nutrition Examination Survey (NHANES) found that serum lycopene is inversely related to prostate cancer risk in both US blacks and whites. The patterns for carotenoids were also similar, except that serum lycopene levels were significantly lower in black men. Differences in lycopene exposure may contribute to the racial disparity in prostate cancer incidence (88). Lycopene may be particularly important in preventing small lesions from developing into more aggressive and lethal forms of this cancer (89), which is the variant seen in African Americans. In a case-control study that compared lifestyle risks of prostate cancer in American men living in South Carolina, increasing lycopene consumption was

associated with reduced risk only among Caucasians (90). In large case-control study that recruited almost equal numbers of black and white men with prostate cancer, they were able to demonstrate the dietary risk of animal products in black men, but were unable to show any clear association with lycopene-rich foods (26).

Our pilot data showed that African-American men in the Washington DC area consumed tomato-sauce less frequently than African migrants in the same area, $p < 0.001$ (Table 1) and that they ate smaller serving portions, 16(44.5%) vs. 22(59.4%) consuming 2-4 serving spoons, $p < 0.08$. When we compared prostate cancer cases with controls there was indication that the cases ate less meals that included tomato-sauce. (Table 2).

Table 1:

Annual Frequency Consumption of Tomato-Sauce / Spaghetti Sauce by Ethnicity						
Annual Consumption Frequency	African-Americans		African Migrants		Total	
	No	%	No	%	No	%
None	12	33.3	2	5.4	14	19.2
Few Times / Yr.	8	22.2	3	8.1	11	15.1
1-2 Times / Month	11	30.6	5	13.5	16	21.9
1-2 Times / Week	3	8.3	6	16.2	9	12.3
3-4 Times / Week	2	5.6	7	18.9	9	12.3
5-7 Times / Week	0	0.0	12	32.4	12	16.4
2 or More Times/ day	0	0.0	2	5.4	2	2.7
Total	36		37		73	

$p < 0.001$

Table 2:

Frequency (%) of Annual Consumption of Selected Cooked Tomato-Based Food Items: Differences between Prostate Cancer Cases and Controls				
Food Items/Meals (Weekly Consumption)	Cases N = 16	Controls N = 37	Total N = 53	p - val
Tomato-sauce ≥ 3 / Wk	6.3	58.3	42.3	0.002
Rice ≥ 3 / Wk	37.5	75.7	64.2	0.009
Rice + Tomato-Sauce	56.3	83.7	76.3	0.04
Spaghetti ≥ 1 / Wk	12.5	5.4	7.5	ns
Pizza ≥ 1 / Wk	68.8	70.3	69.8	ns

2.7 Lycopene supplement and tomato-sauce diet intervention studies:

With this evidence of the health benefits associated with tomato products, several interventions have evaluated the effects of lycopene on markers of prostate cancer risk. Based on their findings the consumption of tomato products at approximately one serving per day or five servings per week as part of an overall healthy diet has been recommended. It is reasonably presumed that this can reduce the risks of prostate cancer, other malignancies and other chronic diseases in the general population. This review emphasizes the distinction between nutritional prevention of prostate cancer and the use of dietary or nutritional treatments for established prostate cancer (89). A large amount of data supports the use of lycopene and other agents for the chemoprevention of

prostate cancer (91,92). Report from the Health Professionals Follow-up Study suggests that the protective effect of tomato products is stronger in older men and for sporadic rather than familial prostate cancer (93).

Phase I Clinical Trials

Lycopene was used in the treatment of 20 consecutive patients with hormone refractory prostate cancer at the dose of 10mg/day for three months. The authors report that lycopene was effective in reducing PSA and bone pain and increasing patient performance status (94)

Phase II Randomized Clinical Trials

In a non-randomized, placebo-controlled, lycopene intervention, 32 Caucasian patients with localized prostate adenocarcinoma consumed pasta dishes with tomato-based sauce for the 3 weeks prior to their scheduled prostatectomy. The diet goal in this study was 30 mg lycopene per day. Serum and prostate tissue lycopene levels increased, and mean PSA levels decreased, among participants in the diet intervention. Analysis of the prostate tissues found the apoptotic index was higher in hyperplastic and neoplastic cells after the diet intervention (95). This intervention demonstrated an increase in serum and prostate tissue lycopene levels, reduction in both leukocyte and prostate tissue oxidative DNA damage, and a statistically significant reduction in PSA (55). Further analysis of this trial showed that tomato sauce did not affect Bcl-2 expression but decreased Bax expression. Tomato sauce consumption may suppress prostate cancer progression only in a sub-set of patients (96). In a similar intervention among newly diagnosed Caucasian prostate cancer patients were randomly assigned to receive a tomato oleoresin extract containing 30 mg of lycopene (n = 15) or no supplementation (n = 11) for 3 weeks before prostatectomy. Biomarkers of cell proliferation, apoptosis and oxidative stress, lymphocyte DNA oxidation product 5-hydroxymethyl-deoxyuridine (5-OH-mdU) were measured in blood and tissue. The patients that received lycopene had smaller tumors, less involvement of surgical margins and/or extra-prostatic tissues, and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (97-99).

Lycopene has also been used in addition to orchidectomy for the treatment of advanced metastatic prostate cancer in 54 patients in India. Patients were randomized to receive orchidectomy with or without 2 mg lycopene twice daily. The patients in the orchidectomy/lycopene group fared better at the 6- and 24-month time points with statistically significant difference for all considered parameters that included complete and partial reduction in serum PSA, resolution or reduction in bone metastasis, peak flow rate and mortality. Mortality is less in the lycopene group, 13% to 35%, $p < 0.001$ (100). These are mainly short-term dietary interventions among men newly diagnosed with prostate cancer. The authors of a nested case-control did not replicate previous reports of a protective association between lycopene and prostate cancer, rather they suggested potential chemopreventive effect for gamma-tocopherol (72). Studies such as these emphasize the implication of variation in bioavailability of lycopene across food preparation methods. Lycopene may be better absorbed in the presence of olive oil, thus tomatoes cooked with olive oil in the context of complex mixtures found in the diet appear to be more effective than single nutrients like lycopene supplements (101,102).

2.8 We propose this randomized, placebo-controlled phase II pilot trial with the intention of exploring the usefulness of lycopene either as a single nutrient, or as a whole-food extract, in the complementary management of biochemical failure in prostate cancer. Lycopene has been reported to decrease PSA levels in a three-week intervention in pre-prostatectomy patients. This current study will investigate its efficacy in prostate cancer patients with biochemical failure. We will collect biomarker data of oxidative stress, isoprostane, inflammation, IL-6, IGF-1, IGFBP-3, and products of DNA oxidation. We shall also control for changes in other nutrients such as tocopherols

and fatty-acids, body-fat measures, and testosterone levels. This will be a robust method to investigate the modulation of these biomarkers and elucidate possible mechanisms of action of these nutrients in prostate carcinogenesis.

3.0 DRUG INFORMATION

3.1 Tomato-Extract Supplement (Lyc-O-Mato ©) Capsules:

The lycopene soft gel capsules (Lyc-O-Mato®, LycoRed Natural Products Industries, Beer-Sheva, Israel) contain 15 mg of lycopene and some minor carotenoids, phytoene, phytofluene and natural tomato matrix and gelatin. There are no added chemicals or micronutrients. Lyc-O-Mato® is produced from specially bred and cultivated lycopene rich tomato varieties developed in Israel by the late Professor Rafael Frankel. These tomatoes contain 3 times greater lycopene than regular tomatoes. LycoRed's hybrid tomatoes were developed through conventional agro-breeding techniques, without using genetic engineering methods. LycoRed's proprietary production process does not involve the use of chemicals, therefore possibility of chemical contaminants in the capsules has been eliminated. In addition to lycopene, very small quantities of other bioactive molecules are found in the Lyc-O-Mato® capsules. These include other natural constituents of tomatoes, such as tocopherols, phosterols, beta-carotene, phytofluene, phytoene, and zeta-carotene. The capsules do not contain any additives, synthetic or natural.

3.2 Lycopene Tablets: (SAUNDRA PLEASE DEVELOP)

Tablets containing 15 / 30 mgs of lycopene will be constituted at the Meharry Pharmacy to look exactly like the Lyc-O-Mato capsules. The capsule case will be obtained from the purchased from the pharmacy. The brand name is *****

3.3 Placebo-tablet (SAUNDRA PLEASE DEVELOP)

4.0 ELIGIBILITY CRITERIA

4.1 Ethnicity: African-American.

4.2 Diagnosis: Histologically confirmed prostate cancer, treated by radical prostatectomy or radiation, seed implantation or external beam radiation.

4.3 Presentation: Biochemical or PSA failure or relapse.

PSA failure is defined according to treatment received as follows:

-Men who had radical prostatectomy:

Two successive readings, at least one month apart, of PSA \geq 0.4 ng/ml, after initial fall to undetectable level.

-Men who had radiation treatment:

Two successive readings, at least one month apart, of PSA above the lowest value attained (nadir) after radiation.

4.4 Consent: Must sign informed consent to participate in the study.

4.5 Exclusion criteria:

i) Enrolled in diet related trial with overlapping intervention/follow-up period.

ii) Taking supplements that are known to contain lycopene, or any micronutrient supplements other than multivitamins.

iii) Life-expectancy less than 1 year by clinician recommendation.

iv) Mental incompetence

v) Erratic life-style, have 5 or more alcoholic drinks/day

vi) Extensive travel or institutionalized and cannot keep follow-up appointment.

vii) Organ function restrictions.

- viii) Chemotherapy within 4 weeks of starting intervention
 - ix) Hormonal therapy within 4 weeks of starting the intervention.
 - x) Eligible for a higher priority study.
- 4.6 No concomitant therapy of any kind that may influence PSA levels.

5.0 REGISTRATION, CONSENT, RANDOMIZATION AND TREATMENT PLAN

All patients must be registered with the Clinical Trials Office in person or by telephone, Meharry at (615)xxx-xxxx, and VU at (615) xxx-xxxx. Patients must be registered prior to initiation of treatment no more than 5 working days prior to planned start of treatment. Participants will then undergo the informed consent in person before they can be enrolled in the study. After registration, consent, and enrolment, study medication will be ordered directly from the Meharry Hospital Pharmacy at no charge to patients. The Pharmacy will have the randomization schedule, and will dispense either lycopene, Lyc-O-Mato, or placebo, depending on patient's sequence number. Patients will be stratified based on ***** response to previous hormonal therapy:

(JAY & SAUNDRA PLEASE HELP)

- 1) Failed previous hormone therapy.
- 2) Did not fail previous hormone therapy.

Table 3: Study treatment plan

STUDY ARM	AGENT	DOSE, ROUTE	FREQUENCY	DURATION
ARM-A1	Lycopene	30 mg, PO	Daily	6 Months
ARM-A2	Lyc-o-mato®	30 mg, PO	Daily	6 Months
ARM-B	Placebo	--- PO	Daily	6 Months

Patients will be instructed to take one tablet with a meal of their choice, most preferable lunch. If they miss the lunch tablet they may take it with dinner or breakfast the next day. They may also take a tablet with a snack if they forget to take it with the designated meal. Patient will be given a calendar and will be asked to check the appropriate boxes when they take their study tablets. Patients will return their study tablet bottle and the calendar at the time they come for their appointments. A pill count will be made and the pill intake calendar will be placed in patient's study folder by the study coordinator.

6.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

6.1 Potential adverse effects will be monitored, recorded and reported according to NCI guidelines using the NCI Common Toxicity Criteria Version 2. Since these nutritional agents did not have any side effects in previous studies and the duration of intervention is short, we do not expect significant toxicity. There are no previous supplementation studies with 30 mg lycopene administered 6 months or longer. However, 30 mg lycopene is present in 1 cup of tomato paste and in certain Mediterranean countries it is usual to consume that amount of lycopene frequently. Previous lycopene studies administered 30 mg daily over 3 weeks with no adverse effect ***(23) and we do not expect any adverse effect with this common nutrient used at these doses. However, baseline and post-intervention laboratory data including CBC with differential and SMA-12 are routinely obtained as a part of patient care. Patients will have monthly history and physical examinations. No dose modifications are allowed in this study. If adverse effects are observed, the study will be halted until the situation is fully discussed with the medical monitor to either stop the study or amend the protocol for dose modification.

6.2 For treatment or toxicity related questions, please contact James Potts, M.D. at 615-XXXXXXXXXXXX.

6.3 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Clinical Trials Office, and to the IRB. The procedure for reporting adverse reactions is outlined in Section 16.0.

7.0 STUDY DURATION

- 7.1 Patients will stay on the study for six months in the absence of toxicity, or disease progression. Disease progression is defined as increase in PSA as defined in section 10.0, or any increase in evaluable or measurable disease or clinical worsening indicative of progressive disease in the opinion of the treating physician. Patients with untreated prostate cancer who had refused or are not candidates for surgery or radiation therapy at registration may be treated for only three months, if standard therapy is deemed to be medically indicated by the managing physician and/or if a patient chooses to accept local therapy.
- 7.2 Patients who have any moderate or severe toxicity as defined by the NCI criteria attributable to the study supplement will be taken off study. All toxicity will be reviewed by a study investigator and assigned a final grade. Decisions regarding continuation or modification of therapy must be discussed with a principal investigator.
- 7.3 Patients who have progressive disease at any time after the first 4 weeks of intervention will be removed from the study. Please refer to section 10.0 for PSA progression criteria, if PSA is being used as the sole criterion for progression.

8.0 STUDY CALENDAR

Table 4: Data collection and specimen evaluation time line

Laboratory & Other Measures	Data Collection Time Line				
	Baseline Studies	Follow-up Studies:			
		Month-3	Month-6	Month-9	Month-12
Clinical Symptom Assessment	X		X		X
Body-fat measures	X		X		X
Dietary Assessment (FFQ)	X				X
Lycopene	X	X	X	X	X
Isoprostane & IL-6	X	X	X	X	X
5-OHmdU & factor NF-B *	X	X	X	X	X
Serum PSA level	X	X	X	X	X
Tocopherols, fatty-acids	X		X		X
Testosterone (total and DHT)	X		X		X
Plasma IGF-1 and IGFBP-3	X		X		X
CBC with differential SMA-12, electrolytes	X		X		X
X-rays and Scans	X	Repeat as clinically indicated			X

*Additional biomarkers of oxidative stress in peripheral blood lymphocytes include:

1. DNA oxidation products 5-OHmdU
2. Oxidative stress induced nuclear transcription factor NF-B

9.0 STUDY ENDPOINTS AND RESPONSE CRITERIA

9.1 Primary Endpoints

Modulation of serum PSA will serve as the marker of tumor growth. The primary endpoint for the study will be the actual decrease in individual patient serum PSA as well as the proportion of patients achieving PSA stabilization or PSA decrease.

9.2 Intermediate End-Points

- a) Plasma lycopene [Jay: Is lycopene a secondary end-point?]
- b) Biomarkers of oxidative stress 5-OHmdU and 8-isoprostane in plasma
- c) Biomarker of inflammation IL-6

9.3 Secondary Endpoints

The secondary endpoints in this study will be:

- a) Plasma IGF-1, IGFBP-3
- b) Serum Testosterone and DHT
- c) X-ray and Scan [Jay: Is this valid?]

**** I have not worked on this at all, and I am hoping that JAY, IKPEAZU will send their ideas so we can develop this portion)

9.4 Definitions:

- 9.41 Complete PSA response (CR): Normalization of PSA (< 4 ng/ml, except for patients with history of radical prostatectomy where normalization = < 0.4 ng/ml) sustained for 3 successive determinations minimum 2 weeks apart.
- 9.42 Partial response (PR): At least 50% reduction of PSA sustained for at least 2 successive determinations minimum 2 weeks apart.
- 9.43 Stable disease (SD): Does not qualify for CR, PR or PD.
- 9.44 Progressive disease (PD): Two PSA values at least 2 weeks apart with $> 50\%$ increase over the minimum PSA level observed during the study.
- 9.45 Time to Treatment Failure (TTF): From date of registration to date of progressive disease or date off-treatment due to toxicity, refusal or death.
- 9.46 Response Duration (RD): From the date response is achieved until relapse or disease progression.

10.0 STATISTICAL CONSIDERATIONS

In a previous study of soy supplementation in prostate cancer patients, a significant decrease in the rate of rise of PSA was detected, using linear mixed effects modeling for repeated measures to test the hypothesis that soy supplementation reduces or slows the rate of PSA rise (Table 5, Omer K. - get reference).

Table 5. PSA modulation by soy isoflavones in Groups II and III

	Group II (n=18)	Group III (n=17)
Effects	p value	p value
Decrease in rate of PSA rise due to isoflavones	0.03	0.07

Statistical analysis:

Mixed effects models provide a useful alternative to classical multivariate regression techniques for modeling such data. This study model will include random patient-specific intercept and slope to account for the natural heterogeneity in the population. Heterogeneity is expected due to uncontrolled factors affecting the natural course of prostate cancer in the patient population. Fixed effects in this model will include linear and quadratic effects of time, effect of lycopene intervention, and time \times intervention interactions. Logarithmic transformation of the outcome variable will be used to achieve a better model fit. Several structures fitted in the covariance model for the final inference will be selected based on Akaike's Information Criterion (AIC) and Schwarz' Bayesian Criterion (BIC). All analyses will be performed using PROC MIXED in SAS, version 6.12.

Sample Size & Power Calculations

(We Need a Statistician, Jay Help!)

Do we need some of our own pilot data? Table 6 is from Omer Kucuk in a 2-Arm study.

Based on the pilot data estimates it has been determined that the sample size of 20 patients per arm will have 90% power and an overall experiment-wise error rate of 5% to detect the following differences in mean endpoint levels as statistically significant. The detectable differences are calculated using a 2-sided independent sample t-test.

Table 6 : Minimum detectable difference in mean endpoint levels (with 80% power)

Serum Endpoint	Estimate of placebo group mean	Estimate of common standard deviation	Minimum detectable difference in means
ODD	93	36	38.2
Free 8-isoprostane	23	7	7.4
Total 8-isoprostane	142	21	22.3

These minimum detectable differences in means translate to 41%, 32% and 15% change in mean ODD, free 8-isoprostane and total 8-isoprostane respectively after three weeks of isoflavone treatment. Given the observed reductions in our pilot study (*i.e.* 48%, 22% and 15% for mean ODD, free 8-isoprostane and total 8-isoprostane respectively), these are feasible differences to expect between treatment arm and placebo over three weeks. A two-sided 5% significance was used at 80% statistical power to determine the smallest detectable changes in mean endpoint levels that can be detected, given that the various mean endpoint levels may increase or decrease. Based on our expectations of directionality for some of the endpoints, we may have 90% power to detect smaller differences than those presented in Table 6, based on a 1-sided test.

The main effect of lycopene (yes/no), and effect modulation (*i.e.*, interaction) with tumor grade and/or tumor stage will be tested. If either interaction effect upon oxidative stress level (or other intermediate endpoint level) is statistically significant, then a stratified analysis may be necessary. In that case, the effect of lycopene (yes/no) would be evaluated separately in each relevant disease stratum. Significant changes are expected in the biomarkers over 6 months. A total study population of 60 patients should provide adequate PSA and biomarker data to determine significant effect. We plan to enter 70 patients to accommodate a non-compliance rate of approximately 15%. The data will be analyzed based on evaluable patients as well as by intent-to-treat.

11.0 SPECIAL INSTRUCTIONS

11.1 Data collection

Personal and medical information questionnaire, including prostate histology information, will be collected by interview, physical measurements such as height, weight, body-fat percent, waist, hip, mid-arm circumference, biceps, triceps and subscapular skin folds will be completed by a trained research assistant, and the BLOCK FFQ will be self-administered. Total calories, total and saturated fats, lycopene, selected fatty acids, and other micro- and macro-nutrient intake will be estimated from the BLOCK FFQ by Nutritionquest, the nutrition company of the Block Dietary Data Systems.

11.2 Blood sample collection

Fasting venous blood, 30ml, will be collected at each of the 5 study time-points using a multi-draw needle, into three separate tubes (red, yellow and purple top) to provide serum, and plasma to measure PSA, lycopene, and all other biomarkers, and lymphocytes for assessing DNA oxidation products. Pretreatment and post-treatment samples will be stored at -80°C in 1 ml aliquots, total of 9 vials per participant at each follow-up.

12.0 REFERENCES

******* Yet to be revised and completed. See references in proposal.**

13.0 APPENDIX

Consent Form. (None at this time)

Saundra kindly provide first draft from existing consent form.

Appendix 3(i): Isoprostanes (IsoPs) as Biomarkers of Oxidative stress

Presentation by Ms. Milne

Jason Morrow, Ph.D. laboratory at VU

Isoprostanes (IsoPs)

- F_2 -isoprostanes are a stable, robust biomarker of oxidant stress.
- These compounds are generated in large amounts in vivo.
 - Normal levels in all human biological fluids have been defined.

Plasma (free)	35 ± 6 pg/mL
Plasma (esterified)	112 ± 22 pg/mL
Urine	1.6 ± 0.6 ng/mg creatinine
CSF	23 ± pg/mL

- In 2005, the Biomarkers of Oxidative Stress Study (BOSS), found that F_2 -IsoPs as measured by gas chromatography-mass spectrometry are the most accurate index of oxidant stress status.

F_2 -Isoprostanes as a Measure of Oxidant Stress

- IsoP levels are increased in animal models of human diseases and human disorders associated with oxidant stress.

↑ Atherosclerosis
↑ Alzheimer's Disease
↑ Diabetes
↑ Hypercholesterolemia

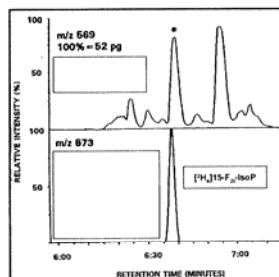
↑ Obesity
↑ Smokers
↑ Ultra-marathon runners

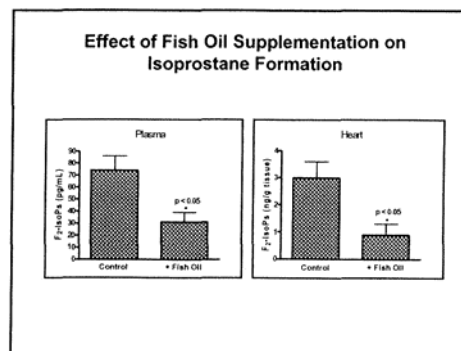
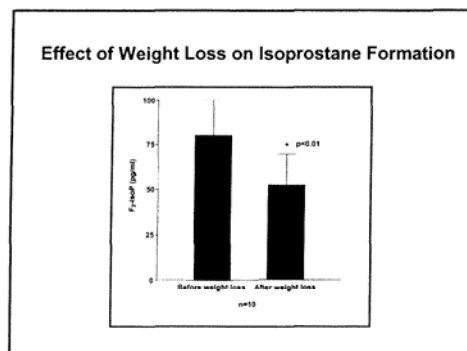
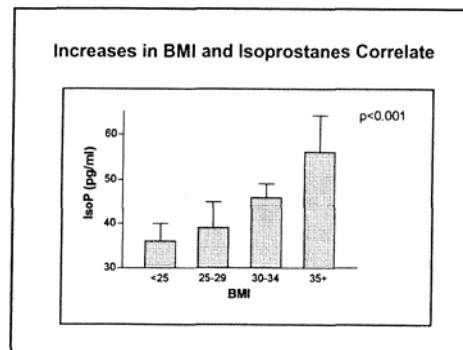
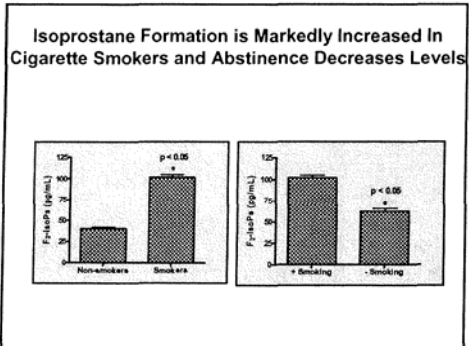
- Deficiencies in antioxidants in vivo are associated with increased IsoP formation.
- Antioxidants and fish oil supplementation decrease IsoP levels in animals and humans.

Sample Preparation for Isoprostane Analysis

Biological fluid or hydrolyzed tissue homogenate
↓
Addition of deuterated standard
↓
Purification by solid phase extraction
↓
Derivatization to pentafluorobenzyl ester
↓
Purification by thin layer chromatography
↓
Derivatization to trimethylsilylether
↓
GC/MS analysis

F_2 -Isoprostanes in Human Plasma





Pros and Cons of Isoprostane Quantification to Assess Oxidant Stress

Advantages:

- Isoprostanes are stable molecules.
- The assay is highly precise and accurate.
- IsoPs can be detected in all fluids and tissues.
 - Normal ranges can be defined.
 - Allows for studies to evaluate the effects of interventions on endogenous lipid peroxidation.

Disadvantages:

- Samples must either be analyzed immediately or stored at -70°C .
- Increases in IsoPs locally in tissues or fluids aren't detected by measuring systemic oxidant stress.
- F_2 -IsoPs represents only one of a myriad of arachidonate oxygenation products.

Available Isoprostane Assays & Requirements

- 8-isoprostane- $\text{PGF}_{2\alpha}$ (also referred to as F_2 -IsoPs)
 - Plasma, 3mL, collect in EDTA containing tubes and store immediately at -80°C , do not thaw
 - Urine, 1mL, Store at -80°C after collection
 - Tissues, 100mg, flash freeze in liquid nitrogen immediately, do not thaw
 - CSF, 1mL, Store at -80°C after collection
- 8-isoprostane- $\text{PGF}_{2\alpha}$ metabolite (urine, 1mL)
- All urinary assays require an additional 0.5mL urine for creatinine analysis.

Appendix 3 (ii) Laboratory Methods for Measuring Hormones Secreted by the Prostate Gland:

Submitted by Anthony Archibong, Ph.D. Reproductive research core laboratory at MMC.

The main cell types distinguished within the normal prostatic epithelium are the secretory luminal cells, the basal cells and the less abundant neuroendocrine cells (Catz and Johnson, 2003). The major cell type is the secretory luminal cell, characterized by the production of prostate secretory proteins, and the expression of the androgen receptor that confers the attribute of androgen-dependent cells. Two of the major proteins produced and secreted by the prostate epithelium secretory cells are PSA (prostate-specific antigen) and PSAP (prostatic-specific acid phosphatase). Both are thought to play a central role in human prostate physiology and pathology. PSA, a human kallikrein with serine protease activity (Yousef and Diamandis 2002) has been shown to contribute to seminal clot liquefaction after ejaculation through hydrolysis of the high-molecular-mass seminal vesicle protein (Lilja, 1985) which is essential for sperm motility. PSAP, a major component of prostatic fluid of unclear physiological function, has also been shown to cleave synthetic peptidyl substrates derived from the sequence of human semenogelins (Brillard-Bourdet et al., 2002). The prostate secretory cells are considered to be the cells of origin of most human prostate adenocarcinomas (Denmeade et al., 1996). Moreover, although the mechanism of secretion by prostate secretory cells remains unclear, several studies have pointed out a connection between the secretory pathways of prostate epithelium and prostate cancer. For example, up-regulation of Rab25 has been related to prostate tumorigenicity (Calvo et al., 2002); a recurrent missense mutant of DOCK4, a GTPase activator, has been found in prostate carcinoma cell lines (Yajnik et al., 2003); PRC17, an oncogene encoding a Rab GTPase-activating protein is amplified in prostate cancer (Pei et al., 2002); furthermore, impaired trafficking has been found to be responsible for a communication deficiency in prostate carcinoma cell lines (Govindarajan et al., 2002). Finally, there is an obvious connection between the secretory products of prostate cells and cancer. First, PSA, which is mainly expressed in the prostate, is often elevated in prostate cancer and is broadly used as a blood-borne diagnostic marker of the disease. Moreover, once secreted, PSA degrades the extracellular proteins fibronectin and laminin (Webber et al., 1995), and this property has been associated with increased invasion by prostate cancer cells. The expression and secretion of PSA are regulated by androgens in normal prostate secretory epithelial cells, and by ErbB-2, MAPK (mitogen-activated protein kinase; Lee et al., 2003) and Akt (Wen et al., 2000) signalling in cells that have become independent of androgen. However, since the secretory machinery that operates during PSA secretion remains elusive, the involvement of these pathways in the regulation of the PSA secretory machinery has not been established, rather, testosterone value can become an adjunct test validating further, the PSA-weighted risk of prostate cancer within the grey diagnostic area (Karamanolakis et al., 2006). Since the observation of Higgins (1941) that disseminated prostate cancer reacts favorably to castration or the administration of estrogenic hormones, first-line hormonal therapy has been used to impair the production or activity of androgens or both. Testosterone is converted to dihydrotestosterone (DHT) by 5 α reductase in the prostate. There have been several studies that examined in detail the method for quantitative analysis of the tissue DHT concentrations of the prostate (Hammond, 1978; Geller and Albert, 1987; Forti et al., 1989; Belanger et al., 1989). Belanger et al. (1989) and Labrie et al. (1993) stated that after the elimination of testicular androgens, the intraprostatic concentration of DHT remains at approximately 40%. These data indicate that a substantial level of DHT remains in the prostate after castration. Belanger et al. (1989) and Labrie et al. (1993) also suggested that DHT completely disappears from the prostate after androgen deprivation therapy with castration and anti-androgen

(flutamide). Nishiyama et al. (2004) demonstrated that the source of androgen for conversion to DHT is not strictly testicular in origin. They showed that DHT in prostatic tissue after androgen deprivation therapy involves intracrine production within the prostate, converting adrenal androgens to DHT. Dihydrotestosterone still remaining in prostate tissue after androgen deprivation therapy may lead to prostate cancer reoccurrence and require new therapies such as treatment with Lycopene, a combination of 5 α reductase inhibitors, anti-androgens and growth factor(s) inhibition.

Handling of Body Fluids For Hormone/Factor Measurements: Prostate specific antigen (PSA), total testosterone, dihydrotestosterone (DHT), steroid hormone binding globulin (SHBG) will be measured in sera collected from research subjects.

Serum extraction from blood and handling: Blood samples will be collected into sterile red top serum separator tubes (BD Vacutainer, Pre-analytical Solution, Franklin Lake, NJ) and delivered to the Core Endocrine Laboratory for processing. Upon arrival in the laboratory, samples will be handled with latex gloved hands during serum separation. Blood samples will be subjected to centrifugation at 500-x g for 10 minutes at 4⁰C, sera harvested (supernatant) and stored frozen at – 20⁰C in labeled 1 ml tubes until assayed for the aforementioned hormones/factors.

Prostate specific antigen: Prostate specific antigen concentrations in each research subject's serum will be determined with a solid-phase immunoradiometric assay (IRMA) kit (DSL 7400) from DSL (Webster, TX). This procedure is based on a two-site IRMA principle. The IRMA is a non-competitive assay in which PSA is “sandwiched” between two antibodies. A captive antibody to PSA is immobilized the inside wall of polystyrene tubes. The other signal antibody is radiolabeled (¹²⁵I-PSA) for detection. Prostate specific antigen present in subjects' sera, standards and controls is bound by both of the antibodies to form a “sandwich” complex during 2 hour incubation at 25⁰C on a shaker set at 180 RPM. Decanting and washing the tubes remove unbound materials and radioactivity in the tubes will be determined with a gamma counter. The PSA concentration in each tube containing subject's serum is directly proportional to the radioactivity present in the tube. Each research subject's concentrations of PSA will be calculated from a calibration curve, which will be run with each assay. A two level control will also be included with each assay run. The functional sensitivity of this assay is 3.0 nmol/L and the mean intra- and inter-assay coefficient of variation is 3.4 % and 8.7%, respectively.

Total Testosterone Assay: Testosterone will be determined using a solid-phase radioimmunoassay, based on testosterone-specific antibodies immobilized to the walls of polypropylene tubes and ¹²⁵I-labeled testosterone as tracer. This assay system is available in a kit form (DSL 4000) and our laboratory routinely uses kits offered by Diagnostic Systems Laboratory Inc (Webster, TX). The incubation period for this testicular steroid assay is 60 minutes at 37°C following which, the fluid content of each tube will be decanted, the tubes dried and counted with a gamma counter and the hormone levels per tube of subject's serum automatically calculated.

The manufacturer's sensitivity for testosterone assay is 0.06 ng/ml and the intra- and inter-assay coefficients of variation are 7.8 and 9.1%, respectively and we intend to follow the manufacturer's instructions without deviation.

Dihydrotestosterone (DHT) Assay: Dihydrotestosterone will be measured in serum samples from research subjects using kits from DSL (Webster, TX; DSL 9600). Prior to conducting DHT RIA,

samples will be subjected to an oxidation reaction, extraction with n-hexane: ethanol (98% n-hexane: 2% ethanol) at 25°C. Subsequently, the organic phase containing DHT will be separated from the aqueous phase by centrifugation at 1500-x g for 15 minutes at 2-8°C following which, aliquots of the upper organic phase will be withdrawn, dried and reconstituted with DHT buffer provided in the kit.

Dihydrotestosterone concentrations in reconstituted extracted DHT will be determined using a solid-phase radioimmunoassay, based on DHT-specific antibodies immobilized to the walls of polypropylene tubes and ¹²⁵I-labeled DHT as tracer. The incubation period for this testosterone metabolite assay is 120 minutes at 25°C following which, the fluid content of each tube (except total count tubes) will be decanted, rinsed once with deionized water, drained to dryness and counted with a gamma counter and the hormone levels per tube of subject's serum automatically calculated.

The manufacturer's sensitivity for DHT assay is 4.0 ng/ml and the intra- and inter-assay coefficients of variation are 3.1 and 8.4%, respectively and we intend to follow the manufacturer's instructions without deviation.

Steroid Hormone Binding Globulin (SHBG) Assay: Steroid hormone binding globulin concentrations in each research of subject's serum will be determined with a solid-phase immunoradiometric assay (IRMA) kit (DSL 7400) from DSL (Webster, TX). This procedure is based on a two-site IRMA principle. The IRMA is a non-competitive assay in which SHBG is "sandwiched" between two antibodies. A captive antibody to SHBG is immobilized the inside wall of polystyrene tubes. The other signal antibody is radiolabeled (¹²⁵I-SHBG) for detection. Steroid hormone binding globulin present in subjects' sera, standards and controls is bound by both of the antibodies to form a "sandwich" complex during a 2 hour incubation on a shaker set at 180 RPM at 25°C. Decanting and washing the tubes remove unbound materials and radioactivity in the tubes determined with a gamma counter. The SHBG concentration in each tube containing subject's serum is directly proportional to the radioactivity present in the tube. Each research subject's concentrations of SHBG will be calculated from a calibration curve, which will be run with each assay. A two level control will also be included with each assay run. The functional sensitivity of this assay is 3.0 nmol/L and the mean intra- and inter-assay coefficient of variation is 3.4 % and 8.7%, respectively.

Insulin-like Growth Factor-1 (IGF-1) Assay: Insulin-like growth factor-1 will be measured in serum samples from research subjects using kits from DSL (DSL 5600; Webster, TX). Prior to assaying samples for IGF-1, this growth factor will be extracted from samples according to the manufacturer's instructions, with reagents provided in the kit. The concentration of IGF-1 per specific volume of sera will be determined using a solid-phase radioimmunoassay, based on IGF-1-specific antibodies immobilized to the walls of polypropylene tubes and ¹²⁵I-labeled IGF-1 as tracer. The incubation period for this growth factor assay is 180 minutes at 25°C on a shaker set at 180 RPM following which, the fluid content of each tube (except total count tubes) will be decanted, rinsed once with deionized water, drained to dryness and counted with a gamma counter and IGF-1 concentration per tube of subject's serum automatically calculated.

The manufacturer's sensitivity for IGF-1 assay is 27 pg/ml and the intra- and inter-assay coefficients of variation are 1.5 and 3.7%, respectively and we intend to follow the manufacturer's instructions without deviation.

Insulin-like Growth Factor-BP-3 (IGFBP-3) Assay: Insulin-like Growth Factor-BP-3 will be measured in serum samples from research subjects using kits from DSL (DSL 6600; Webster, TX) according to the manufacturer's instructions. Unlike IGF-1, samples will not be extracted prior to the determination of their IGFBP-3 content. Rather, samples with anticipated high or low levels of IGFBP-3 will be diluted 1:100 or 1:50, respectively with IGFBP-3 sample diluent provided in the kit. The concentration of IGFBP-3 will be determined in diluted sera using a solid-phase radioimmunoassay, based on IGFBP-3-specific antibodies immobilized to the walls of polypropylene tubes and ¹²⁵I-labeled IGFBP-3 as tracer. The incubation period for this growth factor assay is 18 to 24 hours at 25°C on a shaker set at 180 RPM following which, the fluid content of each tube (except total count tubes) will be decanted and drained to dryness and counted with a gamma counter and IGFBP-3 concentration per tube of subject's serum automatically calculated. The sensitivity for IGFBP-3 assay is 0.5 ng/ml and the intra- and inter-assay coefficients of variation are 3.2 and 1.9%, respectively.

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Appendix 3 (iii)

Measures of Biomarkers of Inflammation

Submitted by Dr. Marshall

High-sensitivity C-reactive protein (hsCRP): this is a standard general marker of inflammation. hsCRP is not a specific prostate cancer biomarker but it is a standard measure of inflammation and, as a pro-inflammatory response is considered to underlie many disease processes, it is commonly used as an indicator of the total amount of inflammation in the body. It is an acute phase protein synthesized by the liver during inflammation and remains elevated until inflammation subsides, after which it takes several more days for CRP levels to decline.

hsCRP..\$8.13/sample x 36 samples x 3 timepoints = \$878.00

hsCRP \$8.13/sample x 36 samples x 5 timepoints = \$1463.40

Interleukin 6: IL-6 is a proinflammatory cytokine that is also a broad measure of inflammation in the body. IL-6 expression is increased via any of a number of proinflammatory cytokines, e.g. TNF α . IL-6, in turn, functions in a proinflammatory and proliferative way via NF κ B. Lycopene has been shown to be effective in suppressing prostatic IL-6 in the Dunning prostate cancer model (Siler et al, 2004) and in normal rat prostate(Herzog et al, 2004).

IL-6 ELISA from eBioscience Cat #88-7066-86

The pricing on this kit is such that whether 3 timepoints or 5 points are measured per sample, the total cost is \$415.00.

TNF α /IL-10 and/or IFN γ /IL-10 ratio: TNF α and IFN γ are both proinflammatory cytokines and IL-10 is an anti-inflammatory cytokine. To maintain homeostasis, the immune system operates with a balance of pro- and anti-inflammatory cytokines until it needs to go in one direction or the other. The ratio of the balancing act is a better measure of distance from homeostasis than the pro-inflammatory response alone. TNF α is one of the molecules that stimulates IL-6 production. Lycopene consumption has been shown to result in decreased serum concentrations of TNF α (Riso et al, 2006).

BD Biosciences ELISA Kits

IFN γ : 3 timepoints for all samples is \$1100.00,

5 timepoints for all samples is \$1650.00

TNF α 3 timepoints for all samples is \$1100.00

5 timepoints for all samples is \$1650.00

IL-10 3 timepoints for all samples is \$1100.00

5 timepoints for all samples is \$1650.00

S100A9: S100A8 (calgranulin A, MRP8)) and S100A9 (calgranulin B, MRP14) are secreted as a heterocomplex (calprotectin) and are proinflammatory. Initially their secretion from neutrophils, macrophages and monocytes was confirmed (Lagasse et al, 1988, Zwadlo et al, 1988, Rammes et al, 1997), then their expression from epithelial cells Gabrielson et al, 1986, Thorey et al, 2001). Strong S100A8 and S100A9 up-regulation has been found in breast, lung, gastric, colorectal, pancreatic, and prostate cancer and in the association with adenocarcinomas, elevated expression of S100A9 within the tumor is correlated with poor differentiation (Gebhart et al, 2006). S100A9 is shown to be a valuable marker for inflammation and serum concentrations are able to discriminate between prostate cancer and BPH at levels where PSA cannot. (Hermani A, 2005).

S100A9 ELISA from Cell Sciences, Inc. Cat # HK325

All samples for 3 timepoints is \$1490.00

All samples for 5 time-points is \$2235.00

IGF1/IGFBP3: insulin-like growth factor 1 is a growth hormone with a pro-proliferative effect. IGFBP3 is one of a number of molecules that modulate IGF1 activity. Large ratios of IGF1/IGFBP3 have been measured in the serum of prostate cancer patients. Lycopene is reported to decrease prostatic IGF1 in rats (Siler et al, 2004, Herzog et al, 2004).

They can be measured by ELISA at the cost of.

DIAGNOSTIC SYSTEMS LABORATORIES, INC.

Cat # DSL-10-2800: IGF1 \$12.00/sample/timepoint x 36 samples x 3 timepoints = \$1,296 total

DSL-10-2800: IGF1 \$12.00/sample/timepoint x 36 samples x 5 timepoints = \$2,160 total

Cat# DSL-10-660: IGFBP3 \$12.00/sample/timepoint x 36 samples x 3 timepoints = \$1,296 total

Cat# DSL-10-660IGFBP3 \$12.00/sample/timepoin x 36 samples x 5 timepoints = \$2,160 total

Inflammation vs Oxidative Damage: Do you need to measure both?

Although I would love to be able to say definitively that you can measure one of these vs the other, I cannot. I don't know enough about the relationship between oxidative damage and inflammation to say. My feeling is that these things go to mechanism and the many ways in which Lycopene appears to have its anti-inflammatory and/or anti-cancer effect. To explain that I think would require a thesis-worth of reading and writing. Chen et al (2001) report that consumption of Lycopene results in decreased oxidative stress, as measured by 8-OHdG levels, in both prostate tissue itself, and in peripheral blood leukocytes. If one of your goal is to generate additional data that goes to mechanism, I believe that you should measure both markers of inflammation AND oxidative damage.

Appendix 4:**Informed Consent Form for MMC****MEHARRY MEDICAL COLLEGE
NASHVILLE, TN 37208***Revised 12/01/2006***INFORMED CONSENT TO PARTICIPATE IN RESEARCH**

PI: Flora A. M. Ukoli, MBBS, DPH, MPH.
Meharry Medical College

Telephone No.: 615-327-5653
Dept.: Surgery

Title of Project: Lycopene Supplementation in the Complementary Management of Biochemical Failure: A Phase II Randomized Trial for African-American Prostate Cancer Survivor.

You are being asked to volunteer as a participant in a research study. This form is designed to provide you with detailed information about this study. If you are eligible and decide to participate in this it will require a total of 6 visits, each one lasting between 30 – 60 minutes.

PURPOSE:

The purpose of this study is to find out if the nutrient supplement, lycopene, can reduce the level of PSA by slowing prostate cancer growth among African-American men whose PSA have started to increase after successful treatment in the past by surgery or radiation. You are being asked to take part in this research study because your PSA level has increased from the very low level attained after your prostate cancer treatment. Several studies suggest that a diet that is rich in lycopene, a nutrient that is found in tomato products, may slow prostate cancer growth and reduce PSA levels. Some studies conducted in human beings have shown promising results, while other studies have not. This study has been designed to compare the effect of two forms of lycopene, one that is a supplement that contains only lycopene referred to as a single-nutrient lycopene supplement, and the other supplement that is derived from pure tomato extract, referred to as a whole-food lycopene supplement. Your urologist is aware of the study, and does not think that your participation will affect the treatment he/she is providing for you. We plan to enroll up to 90 African-American men into this study mainly from Nashville and surrounding counties.

PROCEDURES:

If you agree to be in this study, we will ask you to do the following things. All the activities you will be asked to complete are solely for research purposes. We will ask you to visit our Clinical Research Center (CRC) and after we have determined that you are eligible for the study, we shall require you to register to participate in the study. In this study you will complete questionnaires both written and by interview and you will also provide blood and urine samples for laboratory analysis. If you decide to participate in this study, here is what we will be asking you to do:

- Read and sign one copy of this consent form and return it to the research assistant who will make two copies of the signed form, retain the original in your study file, return one copy to you for your record, and kept one copy in your medical record file. This informed consent process can be conducted at Meharry, your doctor's office, your church or your home.

Patient Initials _____

- Medical Records Review

We would also like to have your permission to review your medical records to obtain information about your prostate cancer, including your PSA at diagnosis, your Gleason score at diagnosis, the size, location, and stage of the tumor, and the treatment that you received for prostate cancer. We will not record information from your record that is not related to prostate cancer.

- Tests and Procedures to be Performed

- Personal, medical and diet information, and measurement of your height, weight, waist, hip, mid-arm circumference, and skin-fold thickness will be collected by a trained interviewer.
- Measurement of your body fat using a special body fat analyzer scale by a trained investigator. This scale cannot be used for men with internal devices like pacemakers.
- This initial study visit will take up to 30 minutes. You will be asked to stop taking any supplements that contain lycopene, because at the end of this visit, we will give you 7 tablets of a non-prescription supplement, and we will ask you to take one-a-day for the following seven days. This is done to be certain that you can safely use the supplements in this study. During this 7-day period, we will call you one time to ask how you are doing, and then call again on the 7th day to ask you the number of supplements remaining.
- If we find you eligible for the study we shall then schedule you for the 1st 30-minute study visit at your convenience.
- You shall receive a call from the study dietician a few days before your visit to complete the 1st of three 24-hour diet recall questionnaire, asking you about the foods you ate the previous day.
- You will receive a urine sample container that will be used to collect your urine sample the morning of your next study visit

1st Study Visit:

- Complete a 2nd 24-hour diet recall questionnaire about the foods you ate the day before the visit. This part of the study will be completed by the study dietician.
- Collection of 30ml (6 teaspoonful) of blood from the vein by a certified nurse to measure PSA, testosterone male hormone, lycopene, lipids, vitamins E, and other research related measures.
- Collection of 5ml (1 teaspoonful) of urine at home on the morning of your office visit, and bring the sample with you to our office. This urine sample will be used to determine the levels of additional hormones that may alter PSA levels. If you smoke tobacco, it is important that this urine sample be collected first thing in the morning before you smoke.
- At the end of this 1st study visit we shall give you 90 lycopene supplement tablets to take daily until your next study visit. A process called 'randomization' will be conducted such that you will be assigned to receive either the single nutrient lycopene or the tomato-extract lycopene. This means you will have an equal chance, like the flip of a coin, of being assigned to any one group. This decision is not made by your doctor or the investigators, and is not based on your medical condition. You cannot choose the supplement type that you prefer. This process will also be 'double-blinded' such that

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you, your doctor, and the study personnel will not know which type of lycopene you are taking as both forms will be made to look the same.

- You will also receive instructions about what to do in case you have any discomfort, pain, feel ill, feel sick, or need to ask any questions.
 - You will receive a urine sample container to be used the morning of your next study visit.
 - You will also be told that we shall call you once a week for the first month, every other week for the second month, and just once in the third month, to ask about your well-being, and to answer any questions.
 - One day during the first week you shall receive a call from the study dietician to complete the 3rd 24-hour diet recall.
- Because we need to collect fasting blood and urine samples from you, you will be scheduled for this 1st study visit between 8.00am – 10.00am. at your convenience, and asked to eat dinner the previous day before 9:00pm and to skip breakfast on the study visit morning. Please do not smoke any tobacco, and do not eat or drink anything until we collect your blood sample. Prior to the study visit we will send you a letter confirming your appointment date and time.
 - A schedule of all your subsequent study visits will be drawn up and one copy will be given to you, one placed in your medical record file, and we shall retain a copy in your study record.

In summary, your research office visit will include

- A blood sample
- A urine sample
- Weight, height, and body measurements
- Questions about your diet in the form of a food frequency and three 24-hour diet recalls.

Study-Visits 2, 3, 4 & 5:

- You will be asked to take one study supplement daily for a total of 12 months, and we shall schedule you study visits every 3 months to collect follow-up information and the urine and blood samples, and to replenish your supplements for 90 days.
- Each of these 4 study visits will be conducted exactly like the first study visit, and will last 30-60 minutes. We shall call you a few days before the visit to complete a 24-hour diet recall, remind you the day before your visit skip breakfast and to collect the urine sample at home, complete questionnaires, complete the 2nd 24-hour diet recall, collect blood and take all your measurements during the visit, record and answer your questions and comments, give you a urine sample container for your next visit, call you a few days after the visit to complete the 3rd 24-hour diet recall, and remind you to call us in case of any problem or illness.
- Your visit will be checked off as completed. The schedule of all your subsequent study visits will be revised at your request, otherwise we shall maintain your scheduled dates.
- Telephone Calls to Measure Your Diet

We will measure your diet using telephone calls throughout the study as described above. This method called the 24-hour diet recall, is the most accurate way to measure what people are eating. During each week in which you are scheduled for an office visit, a dietitian will telephone you and ask you what foods you ate the day before. Each call will require about 15 minutes, and we will ask you for convenient times to call. So you will provide this information

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a few days before a study visit, during the study visits, and within a few days after the study visit. At the end of the study, you may request a summary of all your dietary intake information, with a brief description of what they mean.

- **Study Incentive:** We realize that we are asking you to share your personal, medical and dietary information, asking you to take a study pill for a whole year, and to visit us a total of 6 times, each time lasting 30 – 60 minutes. We are also asking you to respond to several phone calls during this period, ten 15-minute calls to talk about your diet, and other calls to schedule appointments and ask you how you feel. This is indeed a large time commitment on your side, and in appreciation and recognition of your time and effort in participating in this study and the inconvenience of blood and urine sample collection, you will be compensated a total of \$120.00 cash for completing the study, in addition to gift items worth \$20.00. The study incentives will be prorated such that you only receive incentive for the portion of the study that you completed if you decide to discontinue participation before completing all the study procedures, interviews and questionnaires.

The cash incentive is provided towards the cost of transportation and parking, and the inconvenience of the blood draw, while the study promotional ‘Thank-you’ gifts are presented in appreciation of your time and commitment to the completion of the study. Compensation for participating will be prorated as follows:

Cash incentive:

-Initial visit:	\$10
-1 st Study visit:	\$30
(Blood draw, questionnaires, and BLOCK FFQ)	
-Follow-up study visits (4 time-points) @ \$20	\$80
At 3-, 6-, 9-, 12-month	
(Blood draw, questionnaires, and FFQ-T)	

Gift incentive:

-T-Shirt:	At recruitment	(\$10.00)	\$20
-Mug:	At 6-month time-point	(5.00)	
-Certificate/Pin:	At study conclusion	(5.00)	

COST TO YOU:

All these procedures are carried out solely for the purpose of research at no cost to you.

RISKS/DISCOMFORTS:

1. Side effects and risks that you can expect if you take part in this study: The diet supplement is prepared from the active ingredient, lycopene, that is found in some fruits and vegetables, especially in tomatoes. Multivitamins sold across the counter do contain lycopene, and lycopene supplements similar to the ones used in this study are also available in pharmacy stores and on the internet. The general public, prostate cancer survivors, men who believe that this supplement can provide prostate health, and participants in other lycopene supplement research studies take them without any serious side effects. During the study you will be asked not to take any supplements containing lycopene. We will ensure that you are in regular contact with the project staff, and we will encourage you to call if you suspect any side effects. If any side effects persist, you may be advised to take the supplement less frequently or you will be withdrawn from the study.

Patient Initials _____

2. Blood will be collected in the usual way, by inserting a needle into a vein in your arm. Sometimes inserting the needle causes some discomfort or slight pain, but this discomfort or pain should last only a moment. A possible complication of collecting blood is bleeding or the development of a small bruise at the point of needle insertion. Direct pressure at the point of injection will stop this bleeding, and this usually heals without permanent damage. Blood will be collected using sterile equipment to minimize the risk of infection, and by a trained and certified phlebotomist. Very rarely, people feel faint after providing a blood sample. We will monitor you for at least 10 minutes to make sure that any bleeding has stopped and that any feelings of fainting have passed.

3. Risks that are not known: Because this supplement is investigational, meaning non-FDA approved, there may be unknown or unforeseeable risks associated with participation. That is why we plan to monitor and document any such occurrences as accurately as possible with your cooperation.

INJURY / COMPENSATION:

Who to call for any questions or in case you are injured: You should report any injury or illness that you believe to be related to this research project to the project nurse-coordinator Lavenia Crutcher at 615-327-5651, or Dr. Flora A. Ukoli at 615-327-5653, or to James L. Potts, M.D., Chair of the Meharry Institutional Review Board and Office of the Human Protections Administrator at 615-327-6703.

Payment in case you are injured while in this study: Immediate necessary care for such injury, illness or adverse events that occur because of your participation in this research project, will be provided at Nashville General Hospital at Meharry without any charge to you. Meharry Medical College, the research sponsor, and their agents and employees are not responsible for payment of your medical care beyond immediate necessary care, or for compensation of any expenses associated with research-related illness or injury. This "Compensation" statement does not limit your legal rights, and you do not waive any legal rights by signing this form.

BENEFITS:

Good effects that might result from this study: The potential benefits to you is that this study supplement might inhibit the progression of your prostate cancer, and your PSA might stop to increase, or actually return to the very low levels following your initial surgery or radiation treatment. Also science and society as a whole will benefit from the knowledge and result of this study, and such information will be useful in developing dietary supplement education information for prostate cancer patients in the future.

CONDITIONS OF PARTICIPATION:

Participation in this study is voluntary. This study does not exclude you from receiving other treatments for your condition that are prescribed by your urologist. If other treatments for PSA recurrence become available and you prefer the other treatment you can decide not to be in this study. If you choose not to take part in this study, then you would not have to do any of the things listed above, and this would in no way affect your treatment or medical care at Meharry or with your urologist. If you become upset while participating in the study or your questions now or at any

Patient Initials _____

time are not answered to your satisfaction, you can speak with the Principal Investigator Dr. Flora A. Ukoli, at 615-327-5653 or Derrick Beech, MD., at 615-327-6555. It is possible that you may be removed from the research study by the researchers, if you fail to follow the study protocol or experience adverse reactions. If this occurs, the reason will be explained to you. You may withdraw from the project at any time, and refusal to participate or withdrawal from the study, or removal from the study by the principal investigator will not influence your present or future medical care by the staff of Meharry Medical College/Metro General Hospital/Vanderbilt University, your physician or your urologist.

ALTERNATIVE PROCEDURES:

You may choose not to answer certain questions or may contact the principal investigator Flora Ukoli MBBS, DPH, MPH at 615-327-5653 if later you decide to have your samples or questionnaires destroyed.

CONFIDENTIALITY:

Many safeguards have been put in place to protect your personal and study related information from being released to other persons not outside of the study. Effort will be made to keep your personal information private and confidential but absolute confidentiality cannot be guaranteed. You will be assigned a code number when you register to participate in this study, and the study register will be the key that links your name with this code number. All the information we record about you will be kept in paper and computer files that are labeled only with your code number. Your name will only appear in the hard copy register that will be kept in a locked cabinet in the PI's office, and in a password protected electronic study register saved on the PI's computer. The records from this study will be kept confidential and will not be released to anyone who is not working on the study or used for any other purpose unless you agree to release the records, or if required by law. All completed study questionnaires, interviews, surveys, and laboratory reports will be under lock in Dr. Ukoli's office in a separate set of files when not in use by project staff.

The Institutional Review Board of Meharry Medical College and representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research. Your personal identity will be treated as confidential and will not appear in any computer database or on any published results. Other organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the National Institutes of Health, Federal regulatory authorities, and legally authorized parties. All or part of your medical and research records may be reviewed by the Meharry Institutional Review Board, government agencies, and the Office for Human Research Protections (OHRP).

The results of research tests run on your samples will not be recorded in your medical records and neither you, nor your doctor will receive any information about such results. We may share your samples with other scientists who are studying prostate cancer, but we will not give them

Patient Initials _____

your name or any information that lets them link your sample with you. Should the results of this project be published, you will be referred to only by your study code number. All paper records will be kept in locked cabinets in the Principal Investigator's office for a minimum of 3 years after the study has been completed, and then destroyed.

SUBJECT RIGHTS: Any questions you have involving the research and your rights may be addressed to Flora Ukoli (Principal Investigator), at 327-5653 or James L. Potts, M.D., chair of the Meharry Institutional Review Board, at 327-6703. Your participation in this study is voluntary and you are free to withdraw at anytime without penalty or loss of benefits. You will be given a copy of this form to keep.

STATEMENT BY PERSON AGREEING TO PARTICIPATE IN THIS STUDY

- ☐ I have read this consent form. My questions have been answered, and I freely and voluntarily choose to participate. I understand that I may withdraw at any time.
- ☐ The material contained in this consent form has been explained to me verbally. My questions have been answered, and I freely and voluntarily choose to participate. I understand that I may withdraw at any time.

Please check Yes or No and sign your name, indicating you have freely given your answers and consent:

May we contact you again in the future and ask you to participate in other studies? If you are contacted, you will be presented with a form much like this one that will explain the research and ask for your consent to participate.

☐ Yes

☐ No

(Date) / (Time)

Signature of Patient/Volunteer

(Date)

Signature of Witness

(Date)

Signature of person obtaining consent

Patient Initials _____

**MEHARRY MEDICAL COLLEGE
NASHVILLE, TN 37208**

CONSENT FORM FOR BLOOD & URINE SAMPLE DONATION

Principal Investigator: Flora A. M. Ukoli, MBBS, MPH. Telephone No.: 615-327-5653
Meharry Medical College Dept.: Surgery

Title of Project: Lycopene Supplementation in the Complementary Management of Biochemical
Failure: A Phase II Randomized Trial for African-American Prostate Cancer
Survivor.

SUBJECT'S NAME: _____
(Please print) (Last) (First) (Initial)

The primary aim of this study does not include production of materials for commercial purposes. However there is always the possibility and potential that the information generated from studies of the blood and urine samples you provide for this study could be used to produce materials of commercial value (commercial applicability) such as educational materials, diet supplements or drugs. The urine specimen you provide will not be used in this study and is being stored along with some of the blood sample for use in future diet related studies of prostate cancer. The future studies will include the evaluation of the role of testosterone and other hormones, processed meat and other nutrients such as selenium, lycopene, vitamin C and vitamin D as risk factors of prostate cancer progression. Your refusal to allow your samples to be stored for future research will not affect your participation in this or any other study.

This is to confirm that you voluntarily and freely donate your urine and blood samples drawn this day to the Meharry Medical College and hereby relinquish all right, title, and interest to the said items. All the stored samples will not contain any personal identifiers. A key that links the specimens to the donors will be retained in a locked file in the office of the principal investigator for ten years after which that key will be destroyed. Only the principal investigator and the research assistant working on the study will have access to that code.

- ☐ I agree to have my blood & urine samples stored for future research.
- ☐ I agree to have my blood & urine samples stored for genetic research.
- ☐ I do not want my blood or urine samples stored for any future / genetic research.

Participant's Signature

Date

Investigator's Signature

Date

Patient Initials _____

Appendix 5:**Consent form for VU****Vanderbilt University Institutional Review Board
Informed Consent Document for Research****Principal Investigator:** Jay H Fowke, PhD**Revision Date:** December 20, 2006**Study Title:** : Lycopene Supplementation in the Complementary Management of Biochemical Failure:
A Phase II Randomized Trial for African-American Prostate Cancer Survivor**Institution/Hospital:** Vanderbilt University Medical Center

This informed consent applies to African-American prostate cancer patients with PSA recurrence.

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

The purpose of this study is to find out if the nutrient supplement, lycopene, can reduce PSA levels in blood among African-American prostate cancer patients with PSA in the blood. You, and 89 other men are being asked to take part in this research study because your PSA levels have increased from the very low level attained after your prostate cancer treatment. Several studies suggest that a diet that is rich in lycopene, a nutrient that is found in tomato products, may slow prostate cancer growth and reduce PSA levels. Some studies conducted in human beings have shown promising results, while other studies have not. This study has been designed to compare the effect of two forms of lycopene, one that is a supplement that contains only lycopene referred to as a single-nutrient lycopene supplement, and the other supplement that is derived from pure tomato extract, referred to as a whole-food lycopene supplement. Your urologist is aware of the study, and does not think that your participation will affect the treatment he/she is providing for you.

2. What will happen and how long will you be in the study?

All the activities you will be asked to complete are solely for research purposes. This is a 12 month study. You will be asked to take one study supplement daily for a total of 12 months. You will visit the Vanderbilt Clinical Research Center (CRC) for a baseline visit, then again at 3 months, 6 months, 9 months, and 12 months. At each visit, the same activities will be performed. The visits at the CRC will take about 30 -60 minutes. Office visits can be scheduled for a day convenient to you. We will ask that you fast for 12 hours prior to this visit (water only), and therefore this visit should be scheduled in the morning.

Date of IRB Approval:

1 of 6

Date of IRB Expiration:

During each of these visits:

You will complete questionnaires that contain questions about your education, job, your health, as well as your usual activities. We will ask you about the foods you ate the day before the visit.

We will collect a small urine sample (about 1 tablespoon) on the morning of your office visit. You will collect this urine sample at home, and you will bring the sample with you to our office. This urine sample will be used to determine the levels of additional hormones that may alter PSA levels. If you smoke tobacco, it is important that this urine sample be collected at least 2 hours after your last cigarette, cigar, or pipe. We will give you a urine collection cup and written directions on how to collect your urine sample.

We will collect a sample of blood (about 6 teaspoons). This blood sample will be drawn in the usual way, by inserting a needle into a vein in your arm. We will use this blood sample to determine PSA levels, lycopene levels, and other hormones.

We will measure your height and weight, waist, hip, and mid-arm circumference, and thickness of your skin on your back. You will stand on a scale designed to measure the amount of fat in your body. This scale cannot be used for men with internal devices like pacemakers.

Prior to the start of the 12 month study period, you will be asked to stop taking any non study supplements that contain lycopene. At the end of this visit, we will give you 7 tablets of a lycopene supplement, and we will ask you to take one-a-day for the next 7 days starting tomorrow. This is done to be certain that you can safely use the supplements in this study. During the next 7 days, we will call you once to ask how you are doing, and we will then call again on the 7th day to ask you the number of supplements remaining. If we find you eligible for the study, you will be scheduled for the first study visit. Prior to each study visit we will send you a letter confirming your appointment date and time.

At the baseline visit you will be assigned to an intervention group. These groups are:

- a whole-food lycopene supplement group
- single-nutrient lycopene supplement group

The decision of which group you will be assigned is made by a process called randomization. This means you will have an equal chance, like the flip of a coin, of being assigned to any one group. This decision is not made by your doctor or the investigators, and is not based on your medical condition. You cannot choose the supplement type that you prefer. You will not be told which type of lycopene pill you are taking; the pills look exactly the same. Study investigators and your doctor will not know which pill you are taking. This information will be available to you and to the researchers after the study has ended. This is called double blinding, and is necessary to make sure that the information we collect is as accurate as possible. You will be given 90 lycopene supplement tablets to take daily until your next study visit. You will also receive instructions about what to do in case you have any discomfort or pain or need to ask any questions. You will receive a schedule of all your subsequent study visits.

Telephone Calls

We will call you during the study to ask about your well-being, and to answer any questions.

We will measure your diet using telephone calls throughout the study. This method is the most

accurate way to measure what people are eating. During each week in which you are scheduled for an office visit, a dietitian will telephone you and ask you what foods you ate the day before. Each call will require about 15 minutes, and we will ask you for convenient times to call. At the end of the study, you may request a summary of all your dietary intake information, with a brief description of what they mean.

Medical Records Review

We would also like to have your permission to review your medical records to obtain information about your prostate cancer, including your PSA at diagnosis, your Gleason score at diagnosis, the size, location, and stage of the tumor, and the treatment that you received for prostate cancer. We will not record information from your record that is not related to prostate cancer.

3. Costs to you if you take part in this study:

All these procedures are carried out solely for the purpose of research at no cost to you.

4. Side effects and risks that you can expect if you take part in this study:

The diet supplement is prepared from the active ingredient, lycopene that is found in some fruits and vegetables, especially in tomatoes. Multivitamins sold across the counter contain lycopene, and lycopene supplements similar to the ones used in this study are also available in pharmacies and on the internet. The general public, prostate cancer survivors, men who believe that this supplement can provide prostate health and participants in other lycopene supplement research studies take them without any serious side effects. During the study you will be asked not to take any supplements containing lycopene. We will ensure that you are in regular contact with the project staff, and we will encourage you to call if you suspect any side effects. If any side effects persist, you may be advised to take the supplement less frequently or you will be withdrawn from the study.

Blood will be collected in the usual way, by inserting a needle into a vein in your arm. Sometimes inserting the needle causes some discomfort or slight pain, but this discomfort or pain should last only a moment. A possible complication of collecting blood is bleeding or the development of a small bruise at the point of needle insertion. Direct pressure at the point of injection will stop this bleeding, and this usually heals without permanent damage. Blood will be collected using sterile equipment to minimize the risk of infection, and by a trained and certified phlebotomist. Very rarely, people feel faint after providing a blood sample. We will monitor you for at least 10 minutes to make sure that any bleeding has stopped and that any feelings of fainting have passed.

Date of IRB Approval:

3 of 6

Date of IRB Expiration:

5. Risks that are not known:

Because this treatment is investigational, meaning non-FDA approved, there may be unforeseeable risks associated with participation that we do not know about at this time. We plan to monitor and document any such occurrences as accurately as possible with your cooperation.

6. Payment in case you are injured while in this study:

Immediate necessary care for adverse events will be provided at Vanderbilt University without charge if you are injured because of participation in this research project. Vanderbilt will neither provide for the costs of further treatment beyond immediate necessary care nor provide monetary compensation for such injury.

7. Good effects that might result from this study:

The potential benefits to science and humankind that may result from this study may reveal that a widely available diet supplement could improve prostate cancer treatment or outcomes.

The potential benefits to you from this study are:

This study may improve your health. The supplement might inhibit the progression of your prostate cancer, and your PSA might stop to increase, or actually return to the very low levels following your initial surgery or radiation treatment. However, no benefit can be guaranteed.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to take part in this study. If so, then you would not have to do any of the things listed above. This would in no way affect your treatment or medical care.

9. Payments for your time spent taking part in this study or expenses:

We realize that we are asking you to provide your personal, medical and dietary information, take a study pill for 12 months, provide urine and blood samples, and visit us a total of 6 times. We will also be calling you multiple times during this period. You will be given \$10 for the first visit, \$30 for the baseline visit and \$20 for each following visit for a total of \$120. You will also receive a T-Shirt at recruitment (\$10.00), a mug at the 6 month visit (\$5.00) and at study conclusion, a certificate and pin (\$5.00). These gifts have a value of \$20. You will receive payments at the end of the study for the portions of the study you complete.

Date of IRB Approval:	4 of 6	Date of IRB Expiration:
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10. Reasons why the study doctor may take you out of this study:

It is possible that you may be removed from the research study by the researchers, if for example you fail to follow study protocol or experience adverse reactions.

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Jay H. Fowke, Ph.D., at 615-936-2903.

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

Privacy of Protected Health Information:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies, and can be traced back to you. Using or sharing (“disclosure”) such data must follow federal privacy rules. By signing the consent for this study, you are agreeing (“authorization”) to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Fowke and his study team may share the results of your study and/or non-study linked PSA’s, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, The Institutional Review Board of Meharry Medical College and representatives of the U.S. Army Medical Research and Materiel Command, Vanderbilt-Ingram Cancer Center Scientific Review Committee and representatives of the

Date of IRB Approval:	5 of 6	Date of IRB Expiration:
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American Institute of Cancer Research. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least six years after the study is finished. At that time, the research data that has not been put in your medical record will be destroyed. Any research data that has been put into your medical record will be kept for an unknown length of time.

A decision to not participate in this research study will not affect your treatment, payment or enrollment in any health plans or affect your eligibility for benefits. You will receive a copy of this form after it is signed.

May we contact you again in the future and ask you to participate in other studies? If you are contacted, you will be presented with a form much like this one that will explain the research and ask for your consent to participate.

☐ Yes

☐ No

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date

Signature of patient/volunteer

Consent obtained by:

Date

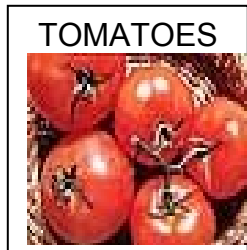
Signature

Printed Name and Title

Date of IRB Approval:

6 of 6

Date of IRB Expiration:



Adverse Events Monitoring Protocol

ID _____

Date _____

Title: Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors

Call subjects as scheduled to actively monitor Adverse Events (AE).

1. Ask questions about the following:

a. ___ difficulty remembering / difficulty thinking clearly

b. ___ tremor

i. ___ muscle weakness

p. ___ gas/flatulence

c. ___ dizziness

j. ___ loss of hair

q. ___ blurry vision

d. ___ nervousness

k. ___ depression

r. ___ eye irritation

e. ___ irritability

l. ___ loss of appetite

s. ___ weight gain

f. ___ fatigue

m. ___ swelling

t. ___ weight loss

g. ___ diarrhea

n. ___ muscle pain

u. ___ dry skin

h. ___ constipation

o. ___ yellowish skin

v. ___ sleep disturbances
(including insomnia)

2. Ask patient if they have any other sign or symptom apart from the ones you have asked about.

a. _____

b. _____

c. _____

3. Remind participant to call the study number anytime they experience any AE, and report the event.

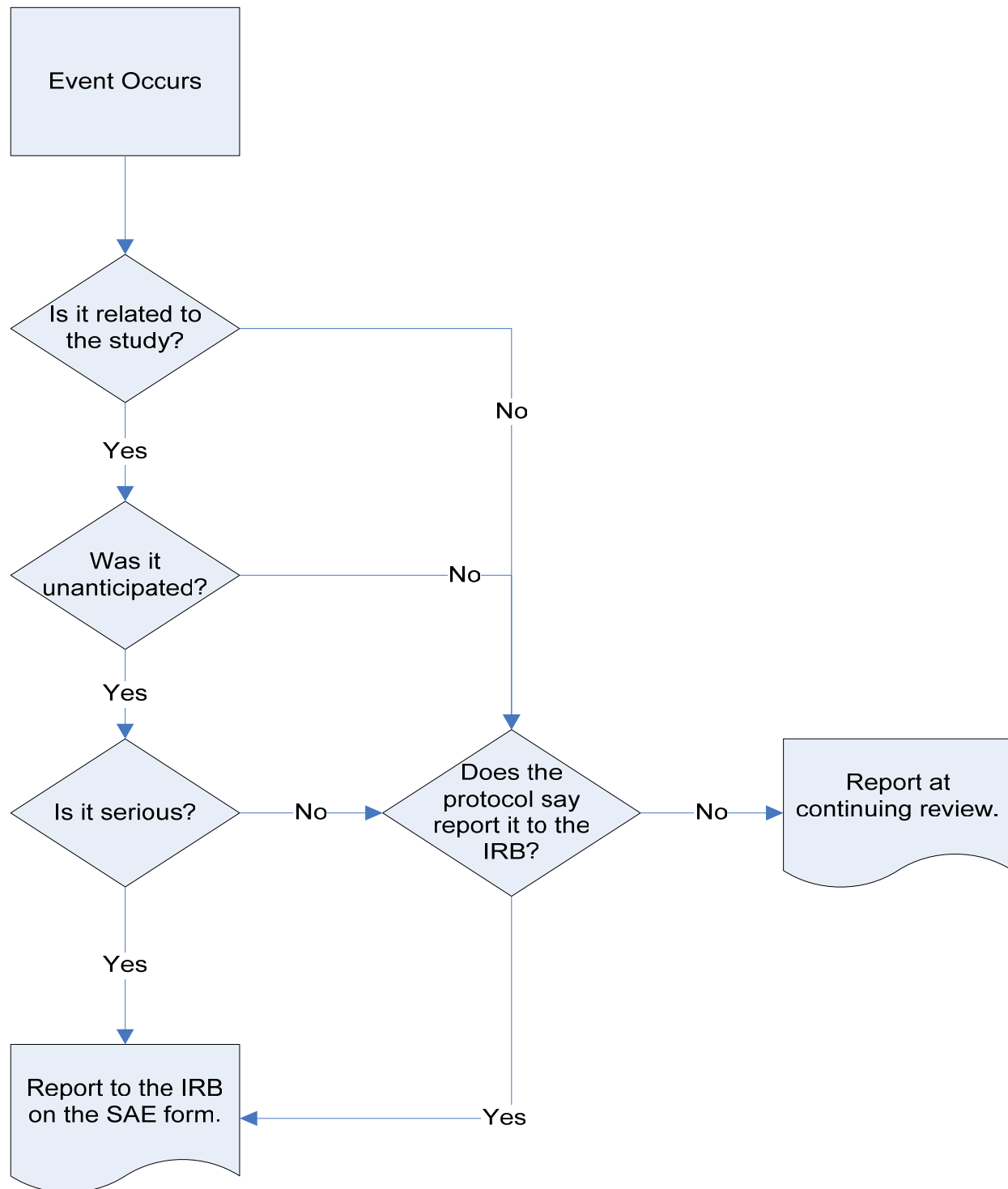
4. Instruct participant not to ever delay seeking emergency treatment in the usual by calling 911, as the AE can be reported after treatment was received.

5. Ask participant to describe action taken and treatment received so far.

a. _____

6. Schedule a doctor's appointment as necessary. _____

Flowchart for PI Reporting Adverse Events Involving Risk to Study Participants



Appendix (iii)

MMC adverse event report form

MEHARRY MEDICAL COLLEGE SERIOUS ADVERSE EVENT FORM

(TO BE COMPLETED BY PRINCIPAL INVESTIGATOR)

Principal Investigator: _____ IRB# _____

Exact Title of Project _____

Subject age: _____ Gender: _____ M _____ F Date of most recent IRB approval _____

New report _____ Follow-up report _____ If Follow-up, date of first report _____

Description of Adverse Reaction: _____

Event onset: _____ Is event continuing: _____ Yes _____ No*

*Event termination: _____

Check all appropriate items:

_____ Resulted in hospitalization or prolonged an existing hospitalization

_____ Resulted in permanent disability

_____ Subject died If so, was an autopsy performed: _____ Yes _____ No

Findings, if relevant (Use additional sheets)

Other: _____

Possibility of this event having been caused by the subject's participation in this study is:

_____ None _____ Low _____ Moderate _____ High _____ Unknown

Action Taken (i.e. describe status of the subject's participation): _____

Cause of event (if not related to research):

_____ Underlying disease _____ Concomitant medication
_____ Disease progression _____ Other: (Describe _____)

Has the same reaction occurred previously in this study? _____ Yes _____ No

If yes, how often? _____

Is event currently listed in consent/assent form? _____ Yes _____ No

Should consent/assent form be revised to inform subject of event? _____ Yes/No

IRB Policy requires submission of internal SAE reports within 48 hours of the PI's knowledge of the event. If this report does not meet this requirement, explain on an additional sheet why it is late.

If YES, attach revised form for review.
If NO, explain why:

Should presently enrolled subjects be informed of event? _____Yes _____No

If yes, have they been informed? _____Yes _____No

Signature of Principal Investigator

Date

NOTE: Submit one original and one copy of this form and a revised consent/assent form, if applicable, to Cynthia G. Weaver or James L. Potts, M.D, Chair of the Institutional Review Board, in the Office of Grants Management. Note: If necessary, submit one highlighted copy of the revised consent/assent form and one clean copy without highlighting.

Is project extramurally funded? _____Yes _____No

If yes, which agency/company? _____

IRB ACTION/OFFICIAL USE ONLY:

Reviewed by: _____ Date _____
Comments: _____

Reviewed by: _____ Date _____
Comments: _____

Reviewed by: _____ Date _____
Comments: _____

IRB Policy requires submission of internal SAE reports within 48 hours of the PI's knowledge of the event. If this report does not meet this requirement, explain on an additional sheet why it is late.

Appendix 7(i): Medical Monitor: Alphonse Pasipanodya, M.D. of Meharry Medical College.

BIOGRAPHICAL SKETCH			
NAME Alphonse T. Pasipanodya, M.D.		POSITION TITLE Associate Professor	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Kutama High School Zimbabwe		1963	
Fisk University, Nashville, TN	B.A.	1967	Biology
Tennessee State university, Nashville, TN	M.S.	1970	Zoology
Meharry Medical College, Nashville, TN	M.D.	1974	Medicine

A. Positions and Honors.

1981-2006 Assistant Professor, Department of Surgery—Meharry Medical College,
2006-Date Associate Professor, Department of Surgery—Meharry Medical College,
2006 Nominated for 2006 Exemplary Teacher Award
1988 Kaiser Permanente Award for Excellence in Clinical Teaching
1972 Meharry Student Research Day, 1972—First Prize
“Some Parameters in Serum of Alloxan Induced Diabetic Rabbits”

CME Credits

2006 Course: “Advanced Inguinal Herniorrhaphy”
Orlando, FL—March 2006
2006 Mini Fellowship for Advanced Laparoscopic Surgery
Charlotte, North Carolina—September 2006
2006 92nd Annual Clinical Congress—October 2006 Chicago, IL

B. Selected peer-reviewed publications (in chronological order).

Hoover, El, Natesha RK, **Pasipanodya, A.**, Sen SK, Weaver WL. Tonsilla Sarcoidosis.
Journal Tennessee Medical Association 1989 March 82 (3) 131-2

A.T. Pasipanodya, M.D. Colorectal Carcinoma—a review of the experience at
Hubbard Hospital

Journal of the National Medicine Association May, 1979, Vol 71 (5) 491-492

A. T. Pasipanodya, Salil K. Das. Some parameters in Serum of Alloxan Induced
Diabetic Rabbits,
FACEB, 1972 (Abstract)

C. Research Support. (Pending)

Lycopene supplementation in the complementary management of Biochemical failure: A
phase II randomized trial for prostate cancer survivors.

Principal Investigator: Flora A. M. Ukoli.

Medical Monitor: Alphonse T. Pasipanodya, M.D.

Appendix 7(ii): Medical Monitor: Alphonse Pasipanodya, M.D.: Support Letter



**SCHOOL OF MEDICINE
SURGERY**

November 1, 2006

Flora A. M. Ukoli, MBBS., DPH., MPH.
(Clinical Epidemiologist)
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37211

Project Titled: "Lycopene supplementation in the complementary management of PSA failure: A Phase II randomized trial for prostate cancer survivors.

I am willing to be the Medical Monitor for this clinical trial. As a physician that is not associated with the protocol, I understand that my role will include reviewing all serious and unexpected adverse events associated with the protocol, and provide an unbiased written report of the event within 10 calendar days of the initial report. At a minimum, I will comment on the outcomes of the adverse event and relationship of the event to the test article, and indicate whether I concur with the details of the report provided by the PI (Flora A. M. Ukoli). I will also be able to provide medical care to research subjects for conditions that may arise during the conduct of the study, if they choose to be treated at this institution. Otherwise they can receive treatment at any other emergency facility. As the medical monitor I will be able to monitor subjects during the conduct of the study.

Sincerely

A handwritten signature in black ink, appearing to read "Alphonse Pasipanodya" with a stylized flourish at the end.

Alphonse Pasipanodya, MD.
Tel: (615) 327-6342
Email: apasipanodya@mmc.edu

Appendix 8 (i):

IRB Application Letter

Date: December 8, 2006.

To: Chairman, IRB
Meharry Medical College

From: Flora A. M. Ukoli, MBBS, MPH.
(Principal Investigator)

Dear Dr. Potts,

RE: Application for IRB approval for Clinical Trial Study Titled:

“Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors”

I wish to submit this proposal titled “Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors” for your kind review. This is the protocol of a Clinical Trial Development Grant funded by the DOD Award Number W81XWH-05-1-0437. The title at that time was “Lycopene supplementation in the complementary management of PSA failure: A randomized placebo-controlled trial for prostate cancer survivors”. The title has been modified to exclude a placebo intervention study arm.

This intervention trial includes the use of two forms of lycopene in the complementary control of PSA biochemical recurrence of prostate cancer following initial treatment success. Since the items to be used in this study are nutrient supplements commonly available over-the-counter, there is no FDA approval necessary to use them. I am expected by the DOD to submit this completed protocol, all study documents to be used in this project, and an institutional IRB letter. In light of the December deadline for the DOD annual report, I am submitting this IRB application as is. The study brochure will be submitted separately.

You can contact me at 1-615-327-5653 if you need additional clarification or information.

Thank you very much.



*SPONSORED RESEARCH
INSTITUTIONAL REVIEW BOARD*

January 17, 2007

Flora A. Ukoli, MBBS, MPH
Surgery
Meharry Medical College
Nashville, TN 37208

RE: *Lycopene supplementation in the complementary management of biochemical failure: a phase II randomized trial for prostate cancer survivors (DOD W81XWH-05-1-0437)*

Dear Dr. Ukoli:

The Institutional Review Board **deferred** your protocol and consent form for the project above at its meeting on January 16, 2007 contingent on the clarifications and corrections below. Corrections to the Human Subject Review Form (HSRF) are to be provided in the form of a revised form and a letter.

Protocol

Has the randomization process been validated by a biostatistician? On page 37, under "m. Reporting Serious or Unexpected Adverse Events," at the end of the 3rd paragraph, last sentence, states "...will stop taking the supplement immediately until a decision to continue or withdrawn from the study is received from the Meharry IRB" is not a valid statement. It is the Principal Investigator's decision when to withdraw the subject from the study, which must be reported to the IRB.

HSRF

When the next submission is presented for review, sign the HSRF and date on page 2.

- 8) The summary is not concise. Strategies and procedures are given in this section. This should be presented in the Protocol section (9A), but no objectives are stated. The summary has to be completely rewritten including formatting. Please reconcile.
- 13) The category of the patient population was not answered or the number of patients that will be recruited. The 2nd section is missing the 2nd sentence. The 3rd section should be "Not applicable" because this question relates to non-English speaking subjects only. Please reconcile.
- 14G) Was answered "No," but is should be "Yes."
- 14H) Please answer the question as it relates to 14G).
- 33) For clarity, use format for the inclusion/exclusion criteria that is located on page 16 of the protocol.
- 34) Rephrase this section since there is no direct benefit in participating in this study.
- 35) What is meant by "inform" in this section. Will this information be provided to the subject with an explanation? Please reconcile.

- 37) The DSMB must be independent and external. The IRB is not the DSMB! Remove mention of the IRB from this section.

Consent Form

Utilize the Meharry template for consent forms when formatting the headings of each section (i.e., Compensation, not Injury/Compensation).

At the end of the Introduction, insert the duration of the study.

Risks. On page 5, #3, delete this section because this is a non-FDA regulated supplement. Injury/Compensation. Replace this section with the Meharry template language for Compensation.

Benefits. Delete the 1st line of this section and replace the 1st sentence with "There may be no benefits. We hope the supplement might inhibit the progression...treatment. Delete the next sentence "Also science...in the future."

Alternative Procedures. Delete the sentence and replace it with "You may choose no to participate in the study.

Page 8. Above the signatory lines, replace all the circles with "Yes and No checkboxes. In the 2nd line, change the end of the sentence to "...stored for genetic (DNA) research."

HIPAA

Under "The Researchers may...with:" will any shared information be shared with Vanderbilt? If so, insert a last bullet point to include "Vanderbilt University."

Telephone Script

Section B: At the top of page 3, how is contact information obtained?

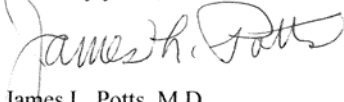
Other

Will there be any advertisements used? If so, they were not submitted with your documentation.

This study may not be started until: A) the investigator has provided the Institutional Review Board with the requested corrections; B) submit 18 copies each of the HSRF, consent form, HIPAA, and tracking changes for the project to be re-reviewed; and C) the project receives final IRB approval.

Please return the requested information to Cynthia Weaver in the Office of Grants Management. Please date all consent forms and indicate that they are revised forms.

Sincerely yours,



James L. Potts, M.D.
IRB Chair

050207FMU042

Introduction

Lycopene Supplementation in Biochemical Failure: A Phase II Randomized Trial for Prostate Cancer Survivors

African-American men have the highest incidence and mortality rates of prostate cancer in the world. Some men who have been treated successfully for prostate cancer can present with biochemical (PSA) recurrence after some years. This may be regarded as the early sign of prostate cancer recurrence. Treatment for this condition includes hormone therapy, surgery or radiation.

Lycopene is a nutrient found in food, especially in tomato. Lycopene has been shown to inhibit the growth of prostate cancer cells by its antioxidant effect. Lycopene has become part of multivitamins taken by men for prostate health. Some clinical trials have shown promising effects of this nutrient at the cellular level, however other studies have not shown any effect on rising PSA. This study is designed for African-American men because they tend to have low blood levels of lycopene, and may therefore benefit by using this supplement during treatment.

The nutrients in whole-foods work together in the body to produce better results. This study will compare the single nutrient lycopene supplement with a whole-food tomato-extract form of lycopene.

Study Protocol

Study Design:

Randomized and Double-Blind Trial. This means that you will be assigned to a treatment arm. Neither your doctor nor yourself nor the researchers can choose the form of lycopene you prefer, and we all shall not know the type of lycopene that you are receiving.

Study Duration: 12 months.

Total number of visits = 6 Visits

Initial visit: Check eligibility.

1st visit: Baseline information

4 Follow-up visits.

Visit schedule: 8.00am -10.00am.

Can schedule visit at other times but will have to make-up an 8:00am (15-minute visit) for sample collection

Visits can take up to one hour.

The following is a schedule of what you will have to do as a study participant at each study visit.

Read and sign:

- *1. Informed Consent
- *2. HIPAA form

Complete a set of questionnaires:

- *1. Personal Information & Medical History
- *2. Food Frequency
- 3. Previous day meals- 3 times
- 4. Quality of Life Assessment

Samples: Skip breakfast

- 1. Blood- 3 sample tubes
- 2. Urine sample

Physical Measurements:

Height
Weight
Mid-Arm Circumference
Waist
Hip
Skin Fold Thickness
Body Fat Percent

* Collected during first visit only.

The study coordinator will call you regularly to monitor the occurrence of any adverse event. You need to call the coordinator and report any pain or discomfort that you feel during this period.

Facts about PSA Failure (Biochemical Recurrence)

Biochemical (PSA) recurrence can occur in patients years after successful treatment of prostate cancer, and is defined as a rising PSA after initial drop to 'normal' after treatment for prostate cancer.

PSA failure is usually diagnosed after 3 successive rises in PSA, and the critical PSA levels for diagnosis depends on the initial treatment:

- After radical prostatectomy: PSA rise from zero to values greater than 0.2 ng/ml
- After radiation treatment: PSA rise by 2.0 ng/ml or more above the lowest value attained.

One third of men treated for localized prostate cancer will develop PSA failure.

Early detection of PSA failure offers the possibility of early intervention by surgery or radiation. This is termed salvage therapy.

Study Director
Dr. Flora A. M. Ukoli

**Meharry Medical College
Clinical Research Center
4th Floor Old Hospital Building
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37208.**



Co-Director
Dr. Jay H. Fowke

**Vanderbilt University
Clinical Research Center
1161 21st Avenue South
Nashville, TN 37232-2195**

For more information

Call: 615-327-5668

615-327-5651

or

Email: fukoli@mmc.edu

For directions to Vanderbilt

Call: 615-936-3418

615-322-6972

***This study is funded by the
U.S. Department of Defense***

Calling!

AFRICAN-AMERICAN PROSTATE CANCER SURVIVORS



LYCOPENE

Complementary Treatment
for

BIOCHEMICAL (PSA) RECURRENCE

**A Phase II Randomized
Clinical Trial**

Cash incentive & Gifts provided.

Budget Justification:

This section describes a three-year budget request over the study period from July 1, 2007 to June 30, 2010. Salaries are based on institutional rates and a 3% yearly increase. Fringe benefits have been calculated for each person, and are calculated at a 3% yearly increase. All costs are rounded to the nearest whole dollar.

Meharry Medical College:**\$115.444****Personnel:**

Flora A. M. Ukoli, MBBS, MPH. Principal Investigator: Flora Ukoli is an Associate Professor and cancer epidemiologist at Meharry Medical College, with a research focus on developing new approaches to reduce cancer risk in the African-American community. She is currently researching the role of body fat and the dietary risk factors of prostate cancer among African-Americans and Africans. The focus of her studies at this time include fatty-acids, lycopene and vitamin E. As the instructor for Epidemiology in the Master of Science in Public Health Program (MSPH) interested students will have the opportunity to participate and train within these projects. This focus is now being expanded to include prostate cancer control by preventing or slowing down progression and reverse biochemical failure. In this study Dr. Ukoli will be responsible for the management and scientific merit of the project. She will develop a clinical recruitment base through liaison with the Nashville General Hospital at Meharry Medical College, Urology Associates, Nashville, the African-American community in Nashville, and through a sub-contract with the urology division of the Vanderbilt University Medical Center. Other urologists in Nashville who attend to African-American patients will also be approached. Dr. Ukoli will supervise the project coordinator (Lavenia Crutcher, RN) and research assistant at Meharry, and oversee the maintenance of IRB approval status of the project through timely periodic review application, and the continuous advertisements for recruitment of eligible men. Having developed the data collection and intervention protocols, Dr. Ukoli will supervise recruitment, eligibility determination, intervention, monitoring of participants, data and sample collection, and data entry processes. Dr. Ukoli will liaise closely with the Co-PI in Vanderbilt, (Dr. Jay Fowke) to ensure that the study procedures at MMC and VU remain identical. Dr. Ukoli will therefore organize and manage staff training, supervise IRB submissions and administration, oversee the management of all recruitment protocols, develop biospecimen and data collection protocols, hold scheduled staff meetings, monitor data collection, implement quality control protocols to evaluate data quality and reliability. She will liaise closely with the five laboratories on the project, supervise shipping of samples to the appropriate laboratories, and receive results of all measurements. Dr. Ukoli and Dr. Fowke will lead data analyses with collaboration from co-investigators to address the study hypotheses regarding the comparative effectiveness of two forms of lycopene supplementation in the inhibition of biochemical failure in prostate cancer progression. (25% Effort)

Rodney Davis, M.D. Investigator. Dr. Davis is an associate professor of Urologic Oncology will head of the Division of Urologic Surgery at Meharry by mid-year. Since he will also have an appointment at Vanderbilt, he will facilitate recruitment of study participants especially at Meharry and also at Vanderbilt. He will also serve as the project urologist and provide clinical expertise in data interpretation and manuscript preparation. Dr. Davis will therefore lead the urologic oncology team of study investigators (Dr. M. Cookson, VU) and other collaborators (Urology Associate urologists), and other private urologists in Nashville who will be involved in this study. He will be able to attract many residents and fellows who are in pursuit of research training into this project.

(10% Effort)

Anthony Archibong, Ph.D. Investigator: Dr. Archibong is an experienced scientist who manages the reproduction core laboratory at Meharry. He will be responsible for the quality of the laboratory analysis of all hormones in the study, and will also be involved in manuscript preparation.

(5% Effort)

Emeka Ikpeazu, M.D., Ph.D. Investigator: Dr. Ikpeazu is an oncologist at the Meharry, and he will develop a strategy to secure the cooperation of other urologists in Nashville. He will develop the follow-up protocol for prostate cancer cases presenting with PSA failure, consult on matters related to care and monitoring the safety of study participant, and provide information to project the potential number of eligible patients seen at the NGH.

(5% Effort)

Derrick Beech, M.D. Investigator: Dr Beech is Professor and Chair of surgery department at Meharry, and will secure necessary institutional support for this clinical trial in addition to contributing to the scientific merit of this proposal. He will identify and secure the support of seminar speakers, urologists and oncologists in Nashville, consolidate strong partnership with the collaborating institutions, and seek institutional cooperation from one other study sites outside of Nashville. This might become an important strategy to meet the recruitment goal of this study.

(3% Effort)

Abu Taher, MBBS, MPH. Post-Doctoral Fellow: Dr. Abu has a very strong medical knowledge background, and he has substantial experience in biostatistical methods. He will directly work with the project coordinators regarding data collection, and will also work with the research assistant to enter the data. Dr. Abu will be trained to implement the study protocols by the PI and Ms. Motley, and will be responsible for processing and storage of biospecimens, a responsibility for which he is already trained. On a daily basis he will contact both study sites (nurse-coordinators), be updated as to the scheduling of study participants, inform the RA accordingly so that they are involved with the day-to-day activities at both research sites. That way they will be able to efficiently coordinate the scheduling of study participants at both sites, receive completed questionnaires, collect and process study samples from the day's recruitment. The post-doc will oversee sample processing, storage, and logging. He will be involved in the development of the database with the PI, plan the data entry training protocol for the research assistant/coordinator, participate in data analysis, and manuscript preparation.

(25% Effort)

Lavenia Crutcher, RN. Project coordinator: Ms. Crutcher is a Research Nurse with extensive experience in clinical nursing, administration, and research nursing at the Meharry Clinical Research Center. She has successfully managed and coordinated several studies in the past and will therefore be responsible for identifying and recruiting study participants, screen them for eligibility, obtained informed consent, oversee the activities of the research assistant regarding study data collection, arrange for the collection of all biospecimens, handover specimen to the post-doc for processing, monitor adverse events in study participants, and conducted medical chart reviews. She will work with the PI to maintain IRB status and documentation, maintain a detailed manual of operations for all study activities, and serve as primary liaison between study investigators and the clinics at Meharry. Ms. Crutcher will be responsible for liaising with the sub-contract coordinator at VU (Ms. Motley) to update progress at that site, and to obtain all study documents and biospecimen for storage at Meharry. To assure consistency across study protocol across project staff, Ms. Crutcher will be familiarized with the study protocol by the PI and Ms. Motley. (12% Effort)

Libnir Telusca, MSPH. Research Assistant: Mr. Telusca will be the administrative assistant at this time, and will provide other research related support for the PI during the study period including to schedule, coordinate and organize meetings, telephone conferences and seminars, and has been trained on the PI's DOD funded project DAMD17-02-1-0068. He has maintained very active and cordial connection with the African-American community, is adept at telephone and face-to-face recruitment into studies. He will therefore receive training in all study protocols from the PI and Ms. Crutcher. Training will continue until all recruitment, consenting, and data collection protocols are consistent. Under the supervision of Ms. Crutcher the RA will assist with organizing recruitment letters, and distribution of study flyers to designated locations. Having received training he will identify eligible men, provide informed consent, recruit, implement data and biospecimen protocols, review questionnaires for completeness, contact participants as needed to confirm unexpected questionnaire responses, obtain medical records for review, and double key-punch questionnaire data and forms into computer databases. Together with the post-doc, the RA will be involved in the daily activities at research sites, and will assist the post-doc with handling biospecimen. Blood for plasma or serum will be centrifuged and aliquoted into adequately labeled cryovials, and stored in designated freezers together with the urine specimen. The RA will ship biospecimens to the appropriate laboratories, maintain computerized tracking logs (sample location, date, aliquots used, and aliquots remaining), and receive laboratory results from the laboratories. Appropriate and accurate labeling, storage and logging is especially important because some of the samples will be stored long-term to be used in future studies. (50% Effort)

Equipment:

\$10,112.

Freezer: The PI already has one freezer, but this will not provide the necessary space for long-term storage of some of the samples from this study for future studies. An additional freezer is therefore required solely for this project. This is the cost for one additional project-specific ultra low temperature, -80°C or colder, upright freezers for long-term storage of plasma, serum, urine, and cells that can be used for DNA extraction in future studies. Based on the number of freezer boxes required to store the samples, we propose a freezer of at least 20 cubic feet in size with a five-year extended warranty (\$8,000) freezer racks necessary to store samples are \$88/rack x 24 racks/freezer (\$2112) = **\$10,112** to be used in year 1.

Supplies:

Computers: One laptop computer is proposed to be used by the RA and post-doc to conduct all project related interviews and data storage. The computer will be protected with a password to allow only the research staff to communicate with colleagues, maintain tracking databases, key-punch data, and manage the day-to-day project activities. The computer must be compatible with the Meharry network. **\$2,000.** The PI has a laptop that can be used at this time, and then the new one will be purchased in year 3. No computer will be purchased in year 1.

File cabinets: This is the cost of two large (at least 5 draws) file cabinets with lockable doors to store all project-related study materials and participant questionnaire data. ($\$800 \times 2 = \textbf{\$1,600}$ in Years 2-3). No file cabinet will be purchased in year 1.

Body Measurement Supplies: This is the cost of one body composition scales to estimate percent body fat and body fat mass in participants. The 310 GS Tanita scale is portable scale with detached input press pads suitable for multi-center recruitment. We already have one BIA scale that is located in the PI's research office, but we require a second one that will remain permanently in the Meharry CRC, the study site for this project. The existing BIA analyzer will be moved as necessary to other locations where patients may be recruited such as Urology Associates. The maximum

weight capacity is 600 pounds that meets our needs, and \$1,895 has been budgeted to pay for this in year 2. A similar scale/analyzer has been budgeted in the first year of the VU sub-award.

Gullick II tape measures provide a reliable means to administer equal tension while measuring body circumferences ($\$45 \times 2 = \90). Free-standing height rods (Seca Model 214) will be maintained at each clinic to ensure a consistently standardized height measure ($\$120 \times 2 = \240), giving a total = \$330. The total cost of the measuring tools will be $\$1,895 + \$330 = \mathbf{\$2,225.00}$, and \$330 will be used in the first year.

Diet assessment supplies: Food models/pictures, food samples, kitchen scale and other diet assessment supplies at \$500 will be spread equally between the first and second years. A set of 200 BLOCK FFQ (Food frequency questionnaires) to be used in the study will cost \$200 only in the first year. The overall total will be **\$700**, and \$450 will be used in the first year.

Blood & Urine Collection Supplies: These are consumable associated with collecting blood samples from the 78 participants across 5 time-points. Blood will be collected for research while subjects are in the recruiting clinic. The clinic research centers (CRC) will provide phlebotomy expertise, but since the blood is being collected solely for research we need to provide project-specific blood collection tubes and blood-drawing adapters. Three 10ml tubes (red-top, yellow-top, and lavender-top) of blood per subject will be collected to provide whole blood, plasma, and serum necessary for DNA extraction and blood analyses. $78 \times 3 \text{ tubes} \times 5 \text{ time points} = 1,170 \text{ tubes} \times \$0.1/\text{tube} = \$117.00$. Blood draw kits, markers, pipettes, swabs, glucostix, etc. will cost \$545. Urine collection containers at \$0.1 per sterile urine cups ($\$0.1 \text{ ea} \times 78 \text{ participants} \times 5 \text{ time-points} = \$39 + \$20 \text{ for } 100 \text{ mg ascorbic acid added as a preservative, giving a total of } \721 . \$396 of this amount is included in the VU budget for that site, and the balance \$325 is budgeted at the site. The amount is spread equally (\$132) in each of the first two years, leaving \$61 for the third year.

All study samples from the VU and MMC sites will be processed at the MMC site. A centrifuge for processing the blood samples will be purchased in the first year for \$885, bringing the overall total for blood and urine collection supplies to **\$1,210**, of which \$1,017 ($885 + 132$) will be used in the first year.

Sample Processing and Storage Supplies:

All the study samples will be stored at the Meharry site. This is the cost of storing blood and urine aliquots at -80° C . Serum ($n=3/\text{subject}$), a clot sample ($1/\text{subject}$), plasma aliquots ($6/\text{subject}$), red cells ($4/\text{subject}$) and urine aliquots ($9/\text{subject}$) will be stored in 1.5 ml cryovials labeled using laser printable freezer vial labels (total = $23 \text{ vials/subject} \times 1170 \text{ subject-time-points} = 26910$ stored in 334 storage boxes ($81 \text{ cryovials/storage box}$)). Total costs across cryovials (VWR 29442-540: $\$0.24/\text{vial} \times 26910 \text{ vials} = \$6,458$), storage boxes (VWR 22250-106: $\$6.6/\text{box} \times 334 \text{ boxes} = \$2,204$), and labels (Shamrock KD5-512: \$256). The total amount is **\$8,918** to be spread unequally across the three years, giving that recruitment will be lowest in the first year. We have budgeted \$2,306 in year 1, and \$3,306 in each of the second and third years.

Project-Specific office supplies, photocopying, printing brochures, and mailing: This is the cost of project-specific notebooks, folders, hanging files, paper, pens, envelopes, postage of research materials and schedule reminders, and other miscellaneous office supplies needed to conduct this research. (\$558). We also budgeted for project-specific photocopying of project questionnaires, recruitment letters, confirmation letters, consent forms, protocols, reminder letters, instructions,

measurements, required administrative documents, brochures etc. This will cost \$0.07/photocopy for the costs of paper, toner, and photocopy machine service for funded research. Based on a calculation of 390 subject-time-points x 80 pages/subject, we budget for 31200 total photocopied pages, = \$2,184, bringing the total for office supplies to **\$2,742**, \$2,566 of which is budgeted in the first year when most of the study materials like brochures and questionnaires will be produced, leaving just \$176 in the third year.

Publication Charges: Publication costs of making pictures of graphs or other items, preparing posters and articles, and also publication expenses either as manuscript submission fees or per page publication fees, or both is budgeted for **\$1,500** in the 3rd year.

Lyc-O-Mato and Lycopene supplements: The tomato extract capsules, Lyc-O-Mato® will be supplied by the Lycored Company while the Lycopene supplement will be purchased commercially. 40 x 2 tablets x 365 days = 29,200 capsules, 292 bottles of 100 capsules @ \$10 = **\$2,922**, spread equally across 3 years, will be \$974 annually.

Table 1. Summary Budget for Materials, Supplies & Consumables Per Study Year

	Year 1	Year 2	Year 3	Total
Computer			\$2,000	\$ 2,000
File Cabinet			\$ 800	\$ 800
Body Fat Analyzer		\$1,895		\$ 1,895
Centrifuge	\$ 885			\$ 885
Measuring Stand + Tape	\$ 330			\$ 330
Diet Assessment Supplies	\$ 450	\$ 250		\$ 700
Blood collection supplies	\$ 132	\$ 132	\$ 61	\$ 325
Blood processing supplies	\$2,306	\$3,306	\$3,306	\$ 8,918
Office supplies, brochures	\$2,566		\$ 176	\$ 2,742
Lycopene supplement	\$ 974	\$ 974	\$ 974	\$ 2,922
Publication costs			\$1,500	\$ 1,500
Total	\$7,643	\$6,557	\$8,817	\$23,017

Travel:

This is to support travel, lodging, per diem, and registration for the PI, post-doc and investigators at Meharry to attend a national scientific conference annually to report study results and to continue medical education. **\$5,400** was budgeted for travel such that the annual travel cost for each of the three years will be \$1,800.

Research Related Patient Costs: Patient incentive.

Participants will receive a total of \$140.00, \$120.00 in cash and gifts worth \$20, only if they complete the study. The cash incentive is provided towards the cost of transportation and parking, and the inconvenience of the blood draw, while the study promotional 'Thank-you' gifts are presented in appreciation of their time and commitment to the completion of the study. Compensation for participating will be prorated as follows:

Cash incentive:

Initial visit:	\$10
1 st Study visit: (Blood draw, Questionnaires, BLOCK FFQ)	\$30
Follow-up visits (4 time-points) @ \$20	\$80
3-, 6-, 9-,12-month: (Blood draw, Questionnaires, and FFQ-T)	

Gift incentive:

T-Shirt:	Recruitment	(\$10.00)	\$20
Mug:	6-month	(5.00)	
Certificate/Pin:	End of intervention	(5.00)	

The total cost for incentives will be \$10,920, \$9,360 in cash and \$1,560 for the cost of gifts. This is necessary to provide participants with transport and parking costs, and to motivate them to remain in the study. It will also improve relationships between researchers and the community, thus building solid trust that will positively impact participation in future research and health promotion activities in this community. All the gifts will be purchased in the first year. Two-thirds of the cash incentive (\$6,240) is within the MMC budget (one-third, \$3,120, is in the VU sub-contract). We plan to use ¼ of the MMC cash incentive amount in the first year, ½ in the second year, and a ¼ in the final year. The total amount for incentives at MMC is **\$7,800**, \$1,560 for the purchase of gifts, and \$1,560 for cash incentives, total \$3,120 in year 1.

Table 2: Summary of Participants Incentive for MMC Site and VU Site

	Year1	Year2	Year3	Total
Meharry				
Gifts	\$1,560	-	-	\$ 1,560
Cash Incentive	\$1,560	\$3,120	\$1,560	\$ 6,240
Subtotal	\$3,120	\$3,120	\$1,560	\$ 7,800
Vanderbilt *				
Cash Incentive	\$780	\$1,560	\$780	\$ 3,120
Total	\$3,900	\$4,680	\$2,340	\$10,920

* See Vanderbilt sub-award.

Other Expenses:

Laboratory analysis of samples:

1. Laboratory analysis will be conducted on a fee-for-service basis at specialized laboratories at the following rates:

-PSA (Free and Total) @ \$40 / sample x 5 time-points = \$200 / participant (ToxMed Laboratories in Nashville. We have worked with them for three years, and this is a discounted rate)

-Lycopene @ \$40/sample x 5 time-points= \$200 / participant (Myron Gross's laboratory at the University of Minnesota.)

-Isoprostane @ 40/sample x 5 time points= \$200/ participant (Jason Morrow's laboratory at VU.)

-Fatty-Acid profile @ \$65/sample x 3 time= \$195/participant (Kennedy Krieger Institute at Baltimore. We have worked with them for over 5 years and this is a discounted rate)

-Testosterone (Free & Total) @ \$40/sample x 5 time-points= \$200/participant (Anthony Archibong core laboratory and MMC). We are in the process of negotiating the inclusion of the measurement of vitamin E at the same time. All samples at all time points for each participants will cost \$995/participant.

Year 1	=	\$995 x 20	=	\$19,900
Year 2	=	\$995 x 40	=	\$39,800
Year 3	=	\$995 x 18	=	<u>\$17,910</u>
				\$77,610

2. Shipping adequately packaged samples by FedEx is budgeted at **\$1,875** for the entire period to

cover the cost of buying appropriate secondary containers for the samples, leak-proof bags for packaging, Styrofoam boxes, the shipping boxes, and the cost of courier delivery service. His amount is spread across the study years as follows, \$375 in the first year, \$750 in the second year and \$750 in year 3.

3. **BLOCK FFQ:** A total amount of **\$3,200** has been budgeted for this section to cover the cost of purchasing FFQ (\$200) that will occur only in the first year, and the cost of analyzing and shipping the FFQs (\$3,000) that is spread equally in the three study years.

Year 1 = \$1,200

Year 2 = \$1,000

Year 3 = \$1,000

4. **Outreach and Advertisement**

Community networking and media advertisement will be conducted in every year of this project. The first year will involve more of the networking and advertisement, and activities will be reduced in the second year, and then boosted in the 3rd year to improve recruitment that usually tends to reduce with time. We plan to be interviewed on television and radio or to be carried as a news item. Also we shall advertise in a popular local newspaper like the Tennessean. Conducting community-based prostate health education activities will also be covered under this section. We budget approximately \$100 each for the planning, organizing, and conducting of these community outreach activities that also serve as forums for distributing study related information and brochures. We budget to provide 10 events in the first year, and 5 events in each of the following years. These events can include a prostate health education presentation, acquiring and distributing prostate cancer educational materials, distributing study brochures, providing free prostate cancer screening for those who have not done so in the previous 12 months, and providing opportunity for questions and answers from those in attendance. We plan to provide some refreshments at these events.

5. **Randomization Costs:** \$300 annually will be the fee for the pharmacist who will be conducting randomization.

Table 3: Summary for 'Other Expenses' Per Year:

Summary expenses	Year 1	Year 2	Year 3	Total
Laboratory analysis	19,900	38,300*	19,410*	19,410
Shipping samples	375	750	750	750
FFQ analysis	1,200	1,000	1,000	1,000
Advertisement	3,500	1,500	2,000	2,000
Community Outreach	1,000	500	500	500
Randomization	300	300	300	300
Total	26,275	42,350	23,960	23,960

*To balance annual total budgets the cost of sample analysis was adjusted accordingly.

Sub-Awards: (Vanderbilt University, University of Minnesota, Wayne State University)

1. Vanderbilt University.

A cost reimbursement sub-award will be made to Vanderbilt University under the direction of Jay H. Fowke, Ph.D, and will mainly include the salary and fringe benefit support for 4 investigators. The sub-award will not be competitive because Jay Fowke is a known collaborator within the Meharry/Vanderbilt Cancer Alliance and is already working on another protocol involving prostate cancer patients. Communication is much easier not only because he is located in Nashville, but because of continued collaboration with the PI on other research and academic activities over the past three years. The total amount of this sub-award is **\$200,974** (direct and indirect costs). Salary efforts are high in the first year when the Co-PI and Nurse coordinator will spend time training the MMC staff, reduce in the second year when the training component would have reduce, and then increase again in the third year when effort will need to intensified to meet the study recruitment goals. Also data analysis and manuscript development will take place in the third year. In the first year this award will be: **\$68,277**

Personnel:

Jay H. Fowke, PhD, MPH, MS. Co-PI: .Dr. Fowke is an Assistant Professor of the Epidemiology Center, Vanderbilt Institute for Public Health, Vanderbilt-Ingram Cancer Center, where he serves as a nutritional and molecular epidemiologist. He will act as the Vanderbilt Co-PI for this project by contributing expertise in the conduct of clinical trials. He has worked with the PI in the preparation of the protocol, consent forms, randomization plan, safety and monitoring plan, among others. He will jointly be responsible for the scientific merit of this clinical trial. Presently Dr. Fowke is PI on studies looking at genetic markers of estrogen metabolism, genetic and endocrine markers of obesity and prostate cancer, and on a diet and diet supplement intervention study targeting prostate cancer patients. Recent publications include the analyses of racial disparities in prostate cancer screening, the effects of obesity on prostate cancer screening, and the relationship between obesity and PSA levels within African-Americans, and the relationship between obesity and prostate volume. He will therefore bring his experience to bear on this clinical intervention with lycopene supplement. In this project he will be responsible for the scientific merit and management of the sub-contract of this project at the Vanderbilt study site. Dr. Fowke will supervise the Vanderbilt site project coordinator (Saundra Motley, RN) and other project-specific staff. Together with the PI (Dr. Ukoli), he will organize project staff training. At the Vanderbilt site Dr. Fowke will supervise IRB submissions and administration, oversee the management of all recruitment protocols, develop biospecimen and data collection protocols, monitor data collection, and implement quality control protocols to evaluate data quality and reliability. He will ensure that all study data and samples are transported as collected to the main study site at Meharry. Dr. Fowke will be fully involved in data analyses and manuscript development in collaboration with the other investigators leading to an increase in his effort to 10.0% in the final year.

(7.5% Effort)

Saundra Motley, RN, MBA. Project Coordinator at the Vanderbilt site: Ms. Motley is a Research Nurse at Vanderbilt, with extensive experience in clinical nursing, administration, and research nursing, and is highly qualified to implement and monitor the project protocols, conduct medical chart reviews, implement the study intervention, and monitor participants for adverse effects

throughout the study. She has served as a very successful project coordinator for an R21 feasibility study under Dr. Fowke, and will bring her experience into this project as she continues to work under his supervision. Ms. Motley has helped the PI to develop the study protocol, study procedure documents, and RB documents, and so is very familiar with this study. Though situated in the sub-contract Ms. Motley holds a very pivotal position on this grant, will therefore act as the main study nurse-coordinator, and will be involved in the training of all the project staff to attain consistency across the study sites. This is why her effort in the first year was boosted to 20%, dropping to 15% in subsequent years when there will be no training. She is familiar with all clinics and clinic staff, at the Vanderbilt University Medical center, and has successfully recruited from Urology Associates, a large private provider in Nashville. Because of financial constraint we cannot afford two RAs on this grant. Therefore Ms. Motley will utilize both the post-doc and the RA to accomplish her project responsibilities. All study data collected will be handled over to the post-doc for data management and storage. Her responsibility will include arranging for biospecimen collection, and will not include processing of biospecimens. Once collected she will handover samples in the provided cooler container to the post-doc or the RA (one of whom will always be present at research activity) for processing at the main study site at Meharry. Ms. Motley will organize distribution of project brochures to all appropriate locations and urology offices, manage the daily recruitment and data collection activities with the research assistant and post-doc, maintain IRB standing and documentation, maintain a detailed manual of operations for all study activities, and serve as primary liaison between the study investigators and the clinics. Ms. Motley will be working under the supervision of Dr. Fowke, and will liaise closely with the PI (Dr. Ukoli) and the nurse-coordinator at MMC (Ms. Crutcher) to ensure consistency across both study sites.

(20% Effort)

Bonnie LaFleur, Ph.D. Investigator: Dr. LaFleur is an outstanding biostatistician with expertise and experience in clinical trials. She has already calculated the appropriate samples size for this study, and has also developed a plan for statistical analysis to compare the two study interventions. Her role will include developing a database for this study, helping to train the post-doc, and the RA to enter data into this database, and familiarize the PI and other investigators with her methods. She will be responsible for data analysis, interpretation, and the development of manuscripts. With the anticipated increase work load in the final year, the biostatistician's effort will increase to 7.5%

(5% Effort)

Jason Morrow, M.D. Investigator: In addition to contributing to the scientific merit of this proposal Dr. Morrow will be responsible for developing a plan to ensure quality control of laboratory assays in this study. He has developed a procedure and a biomarker of oxidative stress in his laboratory, and this study will be using that biomarker to assess the performance and effectiveness of the study intervention in the inhibition of prostate carcinogenesis. This study will depend on Dr. Morrow's laboratory for the measurement of isoprostane at baseline and at all follow-up time-points. He will be responsible for assuring quality control of these measures and will be involved in manuscript development.

(2% Effort)

Michael Cookson, M.D., Investigator: Dr. Cookson is one of the urologists at the Vanderbilt University Medical Center, and he is one of the two project urologists. His responsibility will include bringing the study to the notice of the other urologists in the Urology Division at VU, and also to other urologists in Nashville. He has been involved in consultations with the PI on matters related to management of prostate cancer patients, particularly PSA failure, and the care and safety

of study patients. Dr. Cookson contributed towards the development of the follow-up protocol for the study patients, and provided the clinical outcome measures for adequate follow-up. He will continue to be responsible for developing a working strategy to improve the level of participation of African-American men in this study. He will be available to review patients when necessary, and work with the records section to provide regular estimates of eligible prostate cancer patients seen at Vanderbilt, indicating the proportion with PSA failure and the ethnic distribution. Dr. Cookson will be involved in interpretation of results and the development of manuscripts. (3% Effort)

Supplies and Consumable:

The VU site will receive half of the amount budgeted for office supplies spread equally in the three study years. They will also need to purchase a bodyfat analyzer similar to the type in use in the PI's project at Meharry.

Office supplies and photocopying/year	\$376
Body fat analyzer (one time purchase)	\$1,895
Sub-total	\$2,271
Blood and urine collection supplies	\$132
<u>Total</u>	<u>\$2,403</u>

Research-related patient cost: Participating Patient Incentives:

The VU site will be expected to recruit approximately one-third of the study participants from their clinics, 26 participants @ \$120 cash = \$3120. We anticipate ¼ of the goal to be recruited in each of the first and final years, and ½ in the second year. The budget for the first year is therefore \$780. If this site meets their recruitment goal and are able to recruit additional patients at the site at any time, they will be reimbursed immediately from the MMC budget based on invoice submitted to the PI.

Travel cost:

We have budgeted \$1,800 only in the final year to cover the cost of travel such that the Co-PI and or any other investigators can attend conferences to discuss research progress with peers and to present results at research meetings.

2. University of Minnesota:

\$5,617.

A cost reimbursement sub-award will be made to the University of Minnesota under the direction of Myron Gross, Ph.D, to cover his salary and fringe benefit effort as an investigator on this grant.

Myron Gross, Ph.D. Investigator: Dr. Gross is an established scientist who has developed several studies and written papers on carotenoids including lycopene. He will provide his expertise by overseeing our protocol for sample collection, and all study lycopne assays will be conducted in his laboratory. He will therefore ensure adequate quality control of all the assays. Dr. Gross will be involved in data interpretation and in the development of manuscripts. (3% Effort)

We budget for annual salary and fringe benefit for Dr. Gross with 3% annual increase. We also budgeted \$800 for research related travels in the final year. The total amount of this sub-award will be **\$18,570**, and the amount for the first year is \$5,617.

3. Wayne State University:

\$11,319.

A cost reimbursement sub-award will be made to Wayne State University under the direction of Omer Kucuk, M.D, to cover his salary and fringe benefit support on this grant.

Omer Kucuk, MD., FACN., Investigator: Dr. Kucuk is an oncologist at the Karmanos Cancer Institute, Wayne State University, Detroit, with expertise in nutritional sciences and a lot of experience with prostate cancer related studies using dietary interventions with tomato-sauce and tomato-products, and with dietary supplements in the control of prostate carcinogenesis. He has been involved in the development of this study protocol and has provided consultations on issues related to nutrition, lycopene and prostate cancer. He will be directly involved with the study design, oversee our strategy for monitoring safety of study participants. Having been involved in similar studies he will help the PI to obtain quality tomato-extract supplements, and ascertain the quality of the lycopene supplement that will be used in this study. He will be involved in data interpretation and the development of manuscripts for publication. (3% Effort)

We budget for the annual salary and fringe benefit for Dr. Kucuk with 3% annual increase. We also budgeted \$800 for research related travels in each of the first and final years. The total amount of this sub-award will be **\$33,668**, and the amount for the first year is \$11,319.

Appendix 11. Letters of Support and Biosketch of Investigators



SCHOOL OF MEDICINE

Department of Urology

December 11, 2006

Flora A. M. Ukoli, MBBS., DPH., MPH.
(Clinical Epidemiologist)
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37211

RE: Project Titled : Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors

I have received and read a copy of this proposal and I am willing to participate as an investigator on the project. The study is designed to assess the effect of two forms of lycopene supplementation on prostate cancer progression, at the point of biochemical recurrence. My contribution to the success of this project will include encouraging men with high risk tumors or with biochemical failure to consider participating in this study. I will also talk to my colleagues to encourage their patients to do the same. I will also be available to study participants by appointment to answer questions relating to prostate cancer as the need arises. I will be available for consultations with the PI regarding the safety and monitoring of participants and the development of reports and manuscripts.

Since this is a long-term study with 5 follow-up time-points, it will be important to develop ways of retaining participants' interest. Ensure that participants sign the HIPAA forms along with the consent forms so that information from their medical records can be used in this study.

Sincerely,

A handwritten signature in cursive script that reads 'Rodney Davis'.

Rodney Davis, M.D.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format on preceding page for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Rodney Davis, M.D.	POSITION TITLE Associate Professor of Urology		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Ouachita Baptist University, Arkadelphia, Arkansas	B.S.	1978	Biology
Tulane University School of Medicine, New Orleans, LA	M.D.	1982	Medicine
Madigan Army Medical Center, Tacoma, Washington, DC	Residency	1982-1984	Urology
University of Texas M.D. Anderson Cancer Center, Houston, TX	Fellowship	1994-1996	Urology

A. Positions and Honors

Positions and Employment

1996-present	Associate Professor of Urology, Section of Urological Oncology, Tulane University School of Medicine, New Orleans, LA
1996-present	Chief, Section of Urology, Veteran's Administration Medical Center, New Orleans, L
1992-1994	Chief, Section of Urology, Veteran's Administration Medical Center, Ann Arbor, Michigan
1992-1994	Lecturer, Department of Surgery, Section of Urology, University of Michigan Medical Cent, Ann Arbor, Michigan
1990-1991	Assistant Chief, Residency Training, Madigan Army Medical Center, Tacoma, Washington
1989-1992	Staff, Urologists, Madigan Army Medical Center, Tacoma, Washington

Other Experience and Professional Memberships

1996-present Tulane Cancer Center, Tulane University Medical School
 1996-present Tulane Cancer Center, (Advisory Board) Southwest Oncology (Principal Investigator for Urological Oncology Cancer Committee) V.A. Hospital, New Orleans, LA
 Southeastern Section of the (AUA), American Medical Association (AMA), Louisiana State Medical Society, Society of Urological Nurses and Associates (SUNA), American Association for the Advancement of Science, Michigan Cancer Center, North Central Section of the AUA, Southwest Oncology Group, Reed M. Nesbit Urological Society, American College of Surgeons (ACS), Western Section of the AUA, American Urological Association (AUA), Thirty-Eighth Parallel Society, Puget Sound Urological Society, Society of Government Service Urologists.

HONORS

- 1993 Who's Who Among Outstanding Americans
1994 Veterans Administration's Making A Difference Award
1993 (Silver Cystoscope) Annual Award from the Senior Urology Residents for Excellence

B. Selected peer-reviewed publications.

1. R. Davis, Dingwu Jia, Bekir Cinar, Suresh. C. Sikka, Krishnarao Moparty, Haiyen E. Zhau, Leland W. Chung, Krishna.C. Agrawal and Asim. B. Abdel-Mageed. Functional androgen receptor confers sensitization of androgen independent prostate cancer cells to anticancer therapy via caspase activation. *Biochem. Biophys. Res. Commun.*, 309:937-45, 2003.
2. Flynn V Jr, Ramanitharan A, Moparty K, Davis R, Sikka S, Agrawal KC, Abdel-Mageed AB. Adenovirus-mediated inhibition of NF-kappaB confers chemo-sensitization and apoptosis in prostate cancer cells. *Int J Oncol.* 2003 Aug;23(2):317-23.
3. Usta MF, Adams DM, Zhang JW, Davis R, Hellstrom WJ. Penile epithelioid sarcoma and the case for a histopathological diagnosis in Peyronie's disease. *BJU Int.* 2003 Apr;91(6):519-21.
4. Passarella M, Usta MF, Bivalacqua TJ, Hellstrom WJ, Davis R. Testicular-sparing surgery: a reasonable option in selected patients with testicular lesions. *BJU Int.* 2003 Mar;91(4):337-40.
5. Nugyen A, Jing Z, Mahoney PS, Davis R, Sikka SC, Agrawal KC, Abdel-Mageed AB: In vivo gene expression profile analysis of metallonhionein in renal cell carcinoma. *Cancer Lett*, Nov 28:160(2):133-140, 2000.
6. Halmos G, Schally AV, Sun B, Davis R, Postwick DG, Plonowski A: High expression of somatostatin receptors and messenger ribonucleic Acid for its receptors subtypes in organ-confined and locally advanced human prostate cancers. *J Clin Endocrinol Metab*, July 85(7):2564-2571, 2000.
7. Halmos G, Arencibia JM, Schally AV, Davis R, and Bostwick DG: High incidence of receptors for luteinizing hormone-releasing hormone (LHRH) and LHRH receptor gene expression in human prostate cancers. *J Urol*, 163:623-629, 2000.
8. Navone, N.M., Olive, M., Ozen, M., Davis, R., Troncoso, P., Tu, S.M., Johnston, D. Pollack, A. Pathak, S., von Eschenbach, A.C., Logothetis, C.J. Establishment of Two Human Prostate Cancer Cell Lines Derived from a Single Bone Metastasis¹ *Clinical Cancer Research*. Vol. 3., pp. 2493-2500, December 1997.
9. Davis, R., Chang, S.M., Li, W., Wright, G.L., vonEschenbach, A.C., and Chung, L.W.K.: Clonal Interaction Between Androgen-Dependent (AD) and Independent (AI) Human Prostate Cancer Cells: Role of Androgen and Transforming Growth Factor-Beta. *J. Urol.* 155:606A, 1996
10. Chung, W.K.L. and Davis, R. Prostate Epithelial Differentiation is Dictated by its Surrounding Stroma. *Mol. Biol. Reports*, 23:13-19, 1996.
11. Zhau, H.E., Zhao, L.S., Chung, L.W.K., Chen, B.Q., Troncoso, P., Kao, C., Kojima, M., Symmans, W.F., Zheng, N., Palmer, J.L., Moul, J.W., Davis, R., Ye, M.F., Xiao, L.S., Hall, M.C. Comparative Studies of Prostate Cancers Among U.S., Chinese, and Japanese Patients: Characterization of Histopathology, Tumor Angiogenesis, Neuroendocrine Factors and p53 Protein Accumulations. *Urol. Oncol.* 1:(2) 51-53, 1995.

12. Vaccaro, J., Davis, R., and Hansberry, K. Replacement of Nephrostomy Tubes Using the Ureteroscope. J. Urol. 149:334, 1993.
13. Davis, R., Vaccaro, J., Hodges, G.F., Belville, W., and Kiesling, V. Renal Leiomyosarcoma: A Plea for Aggressive Therapy. Urology 40:168-171, 1992.
14. Moul, J.W., Davis, R., Vaccaro, J., Sihelnik, W.D., Belville, W. And McLeod, D.G. Acute Urinary Retention Associated with Prostate Carcinoma. J. Urol. 141:1375-77, 1989.
15. Vaccaro, J., Davis, R., and Belville, W. Traumatic Hematocele: Association with Rupture of the Testicle. J. Urol. 136:1217-18, 1986.
16. Vaccaro, J., Belville, W., Kiesling, V., and Davis, R. Prostatic Abscess: Computerized Tomography Scanning as an Aid to Diagnosis and Treatment. J. Urol. 136:1318-19, 1986.

In Preparation/Submitted:

1. NMP22 Diagnostic Research Group, Malkowicz SB, Messing EM, Soloway MS, Davis R., et al.: The NMP22 Assay as an aid in the initial detection of urinary tract cancer. Urology (submitted)
2. Myles ME, Ma Q, Davis R., Shenassa B, Sartor O, Espinoza C, Sarwar S, Karabatsos G, and Rayford W: Expression of P27, β -Catenin and TIMP-3 in prostatic tissues of African-American men. Urology
3. Shenassa B, Ruiz-Deya G, Davis R., Thomas R: Ureteroscopic treatment and surveillance of upper urinary tract transitional cell carcinoma: with the use of Holmium:YAG laser. J Endourol
4. Passarella M, Davis R., and Hellstrom WJG: Scrotal exploration: a reasonable option in selected patients with testicular lesions? J Urol (in preparation)
5. Shenassa B, Lacey G, and Davis R.: Prognostic parameters and mortality rate in 31 patients with Fournier's gangrene. (in preparation) Urology
6. Myles ME, Ma Q, Davis R, Shenassa B, Sartor O, Espinoza C, Lorusso G, Karabatsos G, and Rayford W: Human Kallikrein 2 (hK2) expression in prostate cancer: increased expression of angiogenesis factors (VEGF and PD-ECGF) may overcome antiangiogenic action of elevated levels of hK2. Urology (in preparation)
7. Myles ME, Ma Q, Davis R., Shenassa B, Sartor O, Espinoza C, Sarwar S, Karabatsos G, and Rayford W: Characterization of neuroendocrine cell differentiation and distribution in Caucasian and African-American prostate cancer patients. Urology (in preparation)

C. Research Support

Ongoing Resesrch Support

DOD-PC031119: (Abdel-Mageed, P.I.)

1/16/04-1/15/08

"Functional characterization of two novel human prostate cancer metastasis-related genes"

This grant focuses on functional characterization and significance of two novel prostate cancer metastasis related genes recently isolated in my laboratory from metastatic lesions using LCM, SSH and microarray technology.

ACS (Abdel-Mageed, P.I.)

1/1/01-12/31/04

“In Vivo Differentially Expressed Genes of Prostate Cancer: Role of Race, Age and Tumor Grade.

The major objective of this proposal is to isolate and characterize genes that are responsible for bi-racial differences in the incidence and mortality of prostate cancer. There is no overlap with this application.

Role: Co-Investigator

Completed Research Support

NIH (Abdel-Mageed)

9/30/98-9/29/01

R03-DK54971-01

Role of metallothionein in prostate tumorigenesis

Foundation/SWOG

TAP

8/1/99-7/31/01

A randomized prospective study of adjuvant androgen ablation in radical prostatectomy at high-risk for disease recurrence

A Phase II Trial of Cetrorelix in Patients with Advanced Renal Cell Carcinoma (RCC)

Novartis Pharm

11/1/98-10/31/00

Zoledronate Study

SWOG

11/1/99-11/1/00

Urological Cancer Outreach Program Between CTRC Research

Schering-Plough

3/1/00-2/28/01

National phase II trial of Intron, Interferon Alfa 2B plus BCG for the treatment of superficial bladder cancer

TAP/PRA

9/1/00-2/30/01

A phase II, long-term, open-label extension study of oral CEP-701 in patients previously receiving CEP-701 for treatment of prostate cancer

TAP/PRA II

9/1/00-2/30/01

A phase II randomized-discontinuation study of oral CEP-701 in prostate cancer patients who have failed first-line hormonal therapy.



*SCHOOL OF MEDICINE
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY*

August 10, 2006

Flora A. M. Ukoli, MBBS.,DPH.,MPH.
(Associate Professor)
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37211

RE: Project Title: "Lycopene supplementation in the complementary management of PSA failure: A randomized placebo-controlled trial for prostate cancer survivors".

I have received and read a copy of the above-titled proposal and it is a pleasure to be invited to participate as an investigator on the project. My understanding is that this study is designed to assess the efficacy of lycopene in preventing prostate cancer progression in men who have already been treated using lycopene and tomato-extract supplements. Our laboratory will be available for the measurement of testosterone in body plasma or serum samples, and we shall also be able to give advice regarding other study tests.

Looking forward to successful collaboration.

Sincerely

A handwritten signature in dark ink, appearing to read "Archibong", written over a horizontal line.

Anthony E. Archibong, Ph.D.
Assistant Professor and Dir., Core Endocrine Laboratory
Meharry Medical College

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Anthony E. Archibong	POSITION TITLE Associate Professor		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Nigeria, Nsukka, Nigeria	B.Sc. (Hons)	1973	Animal Science
Tuskegee University, Tuskegee, Alabama	M.S.	1979	Reproductive
Oregon State University, Corvallis, Oregon	Ph.D.	1987	Reprod.
N.C. State University, Raleigh, North Carolina	Postdoc.	1987	Embryo Physiology
Oregon National Primate Research Center, Oregon	Postdoc.	1988-1993	Gamete Science

WORK EXPERIENCE:

- 2006-Pres. Associate Professor and Director of Core Endocrine Lab., Dept. of OB/GYN, Meharry Medical College.
- 2003-Pres. Visiting Scholar, Dept of Cell and Developmental Biology, Vanderbilt University.
- 1993-2006 Assistant Professor & Director of Core Endocrine Lab., Dept. of OB/GYN, MMC.
- 1988-1993 Research Fellow, Reproductive Biology and Behavior, Oregon Regional Primate Research Center. 1988-90, Male vaccine-based contraception, Sperm activation and Primate (human and monkey) IVF (Drs. Don Wolf & Dale D. Hoskins, supervisors)
- 1987-1988 Postdoctoral Research Associate (Embryo Physiology), North Carolina State University (Drs. R. M. Petters and B. H. Johnson, Supervisors).
- 1980-1987 Grad. Research Asst. Oregon State University (Dr. F. Stormshak, Major Professor).
- 1986 Predoctoral Fellowship (Maturation of the uterine environment and embryo survival post embryo transfer), USDA, ARS, RLH US Meat Animal Research Center, Clay Center Nebraska (Late Ralph R. Maurer, Supervisor/Mentor)

PATENT APPLICATIONS FILED FOR/AWARDED

Bombesin-like peptides and their receptor antagonists for fertility and contraception.

HONORS, AWARDS AND SOCIETY MEMBERSHIP: (of 18)

- 1983-87 Research Assistantship, Oregon State University
- 1991-93 Reviewer:- J. American Society of Reproductive Medicine
- 1992-Present Reviewer:- Biology of Reproduction
- 1992-Present Reviewer:- Theriogenology
- 2001 Member:- Editorial Board of Advances in Reproduction
- 2001-Present Member:- Editorial Board of Archives of Andrology
- 2000-2004 Member:- Editorial Board of The Society for the Study of Reproduction
- 1998 Recipient: Travel award to attend the "Write Winning Grant" Seminar and Workshop (Tucson, Arizona)
- 2002 National Medical Fellowship (NMF) 2002 Academic Medicine Mentor

SELECTED PUBLICATIONS (of 22)

1. **Archibong, A.E.**, D.C. England and F. Stormshak. 1986. Ovulation and embryonic survival in GnRH treated pubertal gilts Proc. West. Sec. Amer. Soc. Anim. Sci. 37:20-22.

2. **Archibong, A.E., D.C. England and F. Stormshak.** 1987. Factors contributing to embryonic mortality in gilts bred at pubertal estrus. *J. Anim. Sci.* 64:474-478.
3. **Archibong, A.E., D.C. England and F. Stormshak.** 1987. Ovulation and embryonic survival in pubertal gilts treated with gonadotropin releasing hormone. *J. Anim. Sci.* 65:752-755.
4. Gardiner, C.S., A.R. Menino jr., **A.E. Archibong, J.S. Williams, F. Stormshak and D.C. England.** 1988. Suppressed development of cultured mouse and swine embryos by diethylstilbestrol. *J. Anim. Sci.* 66:2401-2406.
5. **Archibong, A.E., R.M. Petters and B.H. Johnson.** 1989. Development of porcine embryos from the one-cell stage to blastocyst in modified kreb ringer buffer supplemented with porcine oviductal fluid. *Biol. Reprod.* 41:1076 -1083.
6. Lanzendorf, S., P. Gliessman, **A. Archibong, M. Alexander and D. Wolf.** 1990. Collection and quality of rhesus monkey semen. *Mol. Reprod. Dev.* 25:61- 66.
7. **Archibong, A.E., R.R. Maurer, D.C. England and F. Stormshak.** 1992. Influence of sexual maturity of donor on in vivo survival of transferred porcine embryos. *Biol. Reprod.* 47:1026 - 1030.
8. **Archibong, A.E., Lee, C.Y.G. and Wolf, D.P.** 1995. Functional characterization of the primate sperm acrosomal antigen (PSA-63). *J. Androl* 16:318 -326.
9. **Archibong, A.E. and S.E. Abdelgadir** (2000). Pharmac-toxicologic Factors and Reproduction: 10. In *Reproduction in Farm Animals* (Hafez, E.S.E., ed.), pp 331-340, Lippincott/Williams/Wilkins.
11. **A.E. Archibong, A.Ramesh and F. Inyang** (2002). Endocrine/environmental factors contributing to early embryonic mortality in gilts mated at first estrus. *Adv Reprod* 6:121-128.
12. S. Mukherjee, S.K. Das, W. Kabiru, K.R. Russell, K. Greaves, A.A. Ademoyero, F. Rhaney, E.R. Hills and **A.E. Archibong** (2002). Acute cadmium toxicity and male reproduction. *Adv Reprod* 6: 143-155.
13. A.Ramesh, F. Inyang, **A.E. Archibong** (2002) Altered imprinting in male rats: a toxicological perspective. *Adv Reprod* 6:156-167.
14. Ramesh, A., Hood, D.B., Inyang, F., Greenwood, M., **Archibong, A., Knuckles, M.E., Nyanda, A.M.** (2002). Comparative metabolism, bioavailability and toxicokinetics of benzo(a)pyrene in rats after acute oral, inhalation, and intravenous administration. *Polycyclic Aromatic Compounds* 22:969-980.
20. **Archibong, A.E., F. Inyang, A. Ramesh, M. Greenwood, T. Nayyar, P. Kopsombut, D.B. Hood, A. M. Nyanda** (2002) Alteration of pregnancy related hormones and fetal survival in F-344 rats exposed by inhalation to benzo(a)pyrene. *Reprod Toxicol* 16:801-808.
16. Inyang, F., A. Ramesh, M. Niaz, P. Kopsombut, D.B. Hood, A.M. Nyanda and **A.E. Archibong.** (2003) Disruption of testicular steroidogenesis and epididymal function by inhaled benzo(a)pyrene. *Reprod Toxicol* 17:527-537.
17. **22.** Inter-species comparison of microsomal metabolism of fluoranthene. 2006.
18. Stormy A.Walker, Linwood B. Whitten, George B. Seals, Whitney E. Lee, **Anthony E. Archibong** and Aramandla Ramesh. *Food Chem Toxicol.* 44:380-7.

SELECTED ABSTRACTS

1. S.L. Stell, **A.E. Archibong, G. Ladson, E. Hills** (2002). Potential embryotrophic activity of porcine oviductal fluid based on estrogen/progesterone content. Presented at the Minority Trainee Research Forum held in San Diego CA.

2. M.A. Sampson, **A.E. Archibong**, G. Ladson, E. Hills (2002). Hydroxyurea influence on embryonic development. Presented at the Minority Trainee Research Forum held in San Diego CA.

3. F. Inyang, A. Ramesh, D.B. Hood, M. Greenwood, M.G. Nunes, P. Kopsombut, A.M. Nyanda, **A.E. Archibong** (2002). Disruption of testicular steroidogenesis and epididymal function by inhaled benzo(a)pyrene. Presented at the Minority Trainee Research Forum held in San Diego CA.
MEHARRY MEDICAL COLLEGE STUDENTS RESEARCH DAY PRESENTATION AWARD WINNING STUDENT ABSTRACTS (2002)

1. Marian A. Sampson (2002). The effect of mimicked in-vivo Hydroxyurea treatment patterns on in vitro embryonic development. Presented at the 2002 annual Student Research Day (**Preceptor**).

2. Antoine Trammell (2002). Non-species specific support for embryo development by porcine oviductal fluid. Presented at the 2002 annual Student Research Day (**Preceptor**).

3. Kea M. Jones (2005). Hydroxyurea treatment of adult males (transgenic mouse model) with sickle cell disease compromises testicular and epididymal function. Presented at the 2004 annual Student Research Day (**Preceptor**).

BURROUGHS WELLCOME TRAVEL AWARD WINNING ABSTRACT (2000)

1. Sylvia Stell, Joe, J. Ford, Mohammad S. Niaz, John R. Diehl, **Anthony E. Archibong** (2000). The effect of porcine oviductal fluid on in vitro development to blastocyst stage by homologous and heterologous embryos. To be presented at the 35th Annual Meeting of the Society for the Study of Reproduction, held at University of Maryland School of Medicine, Baltimore, Maryland (July 27-July 31, 2002).

ABSTRACTS FOR INTERNATIONAL PRESENTATIONS

1. Hydroxyurea treatment of adult males (transgenic mouse model) with sickle cell disease compromises testicular and epididymal function. Kea M. Jones, Maria del Pilar Aguinaga, M. Niaz, V. Williams, C.M. Brooks, T. Turner, and **A.E. Archibong** (2004; Presented at the 37th Annual meeting of the Society for the Study of Reproduction, held at Vancouver, BC, Canada).

2. Sickle cell disease compromises reproductive performance in adult males (transgenic mouse model) C.M. Brooks, K.M. Jones, M.S. Niaz, Maria del Pilar Aguinaga, V.J. Williams and **A.E. Archibong**. (2004; Presented at the 37th Annual meeting of the Society for the Study of Reproduction, held at Vancouver, BC, Canada).

RESEARCH SUPPORT

ACTIVE GRANTS

1) Title: Cooperative Center for Reproduction in Minority Institution (U54/IU54HD0431501-09).

Role: PI of Endocrine Core Lab (% Effort, 20%)

Principal Investigator: PonJola Coney, M.D.

Duration of Grant: July, 2003-June 2008.

Major Goal: to establish infrastructure for reproductive endocrinology research at Meharry Medical College.

2) Title: Sperm function in fertilization events (Minority Supplement, RO1 HD020419-19S1).

Role: P.I. (% Effort, 40%)

Duration: 2003-2007.

Major Goal: to study the maturation of sperm in the epididymis and molecular factors that influence their ability to fertilize mature ova.

3) Influence of benzo(a)pyrene on ovarian function (RCMI/NCRR).

Role: P.I. (% Effort, 25%)

Duration: 2005-2009

Major Goal: to study the endocrine disruptive effects of benzo(a)pyrene on the ability of the ovary to develop and ovulate mature ova, in response to pituitary gonadotropins.



School of Medicine
Internal Medicine

December 11, 2006

Flora A. M. Ukoli, MBBS., DPH., MPH.
(Clinical Epidemiologist)
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37211

RE: Project Titled: Lycopene supplementation in the complementary management of
Biochemical failure: A phase II randomized trial for prostate cancer survivors

I have received and read a copy of this proposal and I am willing to participate as an investigator on the project. The study is designed to assess the effect of two forms of lycopene supplementation on prostate cancer progression, at the point of biochemical recurrence. My contribution to the success of this project will include encouraging men with high-risk tumors or with biochemical failure to consider participating in this study. I will also talk to my colleagues to encourage their patients to do the same. I will be available to study participants by appointment to answer questions relating to prostate cancer as the need arises. I will also be available for consultations with the PI regarding the safety and monitoring of participants and the development of reports and manuscripts.

Since this is a long-term study with 5 follow-up time-points, it will be important to develop ways of retaining participants' interest. Ensure that participants sign the HIPAA forms along with the consent forms so that information from their medical records can be used in this study.

Sincerely,

A handwritten signature in black ink, appearing to read "Emeka Ikpeazu".

Emeka Ikpeazu, M.D., Ph.D., F.A.C.P.
Associate Professor
Division of Hematology/Oncology

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Ikpeazu, Chukwuemeka	POSITION TITLE Associate Professor of Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Nebraska, Lincoln/Omaha, NE	B.S.	1982	Biology
Meharry Medical College, Nashville, TN	Ph.D.	1988	Biomedical Sciences
Meharry Medical College, Nashville, TN	M.D.	1992	Medicine

A. Positions and Honors

Positions and Employment

1992-1994	Mayo Graduate School of Medicine, Internal Medicine Residency, Rochester, MN
1994-1996	Meharry Medical College, Internal Medicine Residency, Nashville, TN
1996-1998	Medical Oncology Fellowship, Johnson City, TN
1998-2000	Hematology/Bone Marrow Transplantation Fellowship, Vanderbilt Univ. Medical Center, Nashville, TN
2000-2004	Assistant Professor of Medicine, Div. Hematology/Oncology, Meharry Medical College, Nashville, TN
2004-present	Associate Professor of Medicine, Div. Hematology/Oncology, Meharry Medical College, Nashville, TN
2000-present	Adjunct Assistant Professor of Medicine, Div. Hematology/Oncology, Vanderbilt University Medical Center

B. Selected peer-reviewed publications (in chronological order)

1. Hardy RE, Ikpeazu EV, Bone Marrow Transplantation: A Review. J Natl Med Assoc. 81(5): 518-523, May 1989.
2. Ikpeazu EV, Valenzuela MS. A unique deletion in pBR322 DNA caused by insertion of Poly (dA). Poly (dT). Plasmid 21, 247-250 (1989).
3. Valenzuela MS, Ikpeazu EV, Siddiqui KAI. E coli growth inhibition by a high copy number derivative of plasmid pBR322. Biochem. Biophys. Res. Comm. 219, 876-883 (1996).
4. Ikpeazu EV, Kaplon MK. Cryptococcal meningitis occurring at 19 months after Cladribine therapy for hairy cell leukemia. Eur. J. Haematol. 1998 Oct. 61 (4): 286-287.
5. Ikpeazu EV, Davidson M, Halteman D, Goodman S, Browning P, Brandt S. Donor origin of circulating endothelial cell progenitors after allogeneic bone marrow transplantation. Biology of Blood and Marrow Transplantation. 6:301-308 (2000).
6. Coates L, Ikpeazu EV, Chen Y, Valenzuela MS. Inhibition of DNA replication by berenil in plasmids containing Poly(dA)poly(T) sequences. Plasmid 2002 Mar; 47(2): 120-8.

Abstracts

1. Ikpeazu, E.V., Valenzuela, M.S.: Construction of Recombinant Plasmids Containing Berenil-Target Sequences. October, 1987. (Abstract #95). NIH Centennial MBRS Symposium. Washington, D.C.
2. Ikpeazu, E.V., Valenzuela, M.S.: Specific Deletions Caused By Insertion of **POLY dA-dT** in pBR322 DNA. May, 1988. American Society for Biological Chemists/Federation of American Society for Experimental Biology (ASBCIFASEB) Meeting. Las Vegas, Nevada.
3. Kumar, P.P. and Ikpeazu, E.V.: Biochemical Response Following External Radiation Therapy in the Treatment of Localized Prostate Cancer. May 16-19, 1998. (Abstract #1295). Proceedings of The American Society For Clinical Oncology (ASCO) 34th Annual Meeting, Los Angeles, Ca.
4. Ikpeazu, E.V., T. Ward, A.B. Kamad.: Problems With PSA-Based Screening For Prostate Cancer In Veterans. May 16-19, 1998. (Abstract #1291). Proceedings of The American Society For Clinical Oncology (ASCO) 34k" Annual Meeting, Los Angeles, Ca.
5. Ikpeazu, E., Vangel, M., Sculler, J.H., Bonomi, P.D., Jolmson, D.H.: Survival in Advanced Non-Small Cell Lung Cancer (NSCLC) with Platinum-Based Chemotherapy in Two Eastern Cooperative Group Trials: The Influence of Race. Submitted for ASCO 2003. Abstract # 104242.

Presentations:

1. Ikpeazu, C, Davidson, MK, Halteman, D, Goodman, SA, Browning, P3, Brandt, SJ. Donor Origin of Circulating Endothelial Progenitors Following Allogeneic Bone Marrow Transplantation. In *Tenth Annual Mayo Clinic Jacksonville Symposium on "State of the Art Treatment of Hematology/Oncology Disorders"*. July 28-30, 2000.
2. Ikpeazu, Emeka; Adegoke, Olufemi; Hulan, Rita: Cancer in Minority Populations: The Metropolitan Nashville General Hospital Experience. The Ninety Ninth Annual Convention and Scientific Assembly of the NATIONAL MEDICAL ASSOCIATION. August 4-9, 2001.
3. Ikpeazu, Emeka: Oncology Clinical Trials at Meharry Medical College-Metropolitan Nashville General Hospital. First Annual Retreat of the MMC-VICC Cancer Partnership. January 13, 2001.
4. Ikpeazu, Emeka: Oncology Clinical Trials at Meharry Medical College-Metropolitan Nashville General Hospital. Second Annual Retreat of the MMC-VICC Cancer Partnership. January 12, 2002.

C. Research Support

Southwest Oncology Group
SELECT S0000, Cancer Prevention of Prostate Cancer with Selenium & Vitamin E Alone and in Combination, Phase III
Role: PI

National Surgical Adjuvant Breast and Bowel Project
NSABP Study of Tamoxifen and Raloxifene (Star) for the Prevention of Breast Cancer
Role: Co-investigator
National Cancer Institute
Title: MINORITY-BASED COMMUNITY CLINICAL ONCOLOGY PROGRAM
Approved: 06/01/04 to 05/31/07
Total costs: \$2,839,794
Role: Co-Principal Investigator



*SCHOOL OF MEDICINE
DEPARTMENT OF SURGERY*

*Derrick J. Beech, M.D., F.A.C.S.
Professor and Chairman*

December 11, 2006

Flora A. M. Ukoli, MBBS., DPH., MPH.
(Clinical Epidemiologist)
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37211

RE: Project Titled : Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors

I support your effort regarding prostate cancer research, and will participate as an investigator on this project. I have established a strong community network, and will be able to spread awareness about the study during my community outreach activities. Another contribution to the success of this project will include encouraging urologists in Nashville to support this effort, and to permit distribution of study brochure in their offices. I will be available for consultations with the PI regarding the safety and monitoring of participants and the development of manuscripts.

This is a clinical trial that requires institutional support, and this will be provided. It is very important for you to have all participants sign the HIPAA forms along with the consent forms so that information from their medical records can be used in this study.

Sincerely

A handwritten signature in black ink, appearing to read "Derrick J. Beech", with a stylized flourish at the end.

Derrick J. Beech, M.D., F.A.C.S.
Professor and Chairman
Department of Surgery
Meharry Medical College

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Beech, Derrick M.D.		POSITION TITLE Professor and Chairman Department of Surgery Meharry Medical College	
eRA COMMONS USER NAME Beechd			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Duke University, Durham, North Carolina	B.A.	1984	Mathematics
Medical College of Virginia, Richmond, Virginia	M.D.	1988	Medicine
Temple University Hospital and Clinics, Philadelphia, Pennsylvania	Internship	1988- 1989	Surgery Intern
Temple University Hospital and Clinics, Philadelphia, Pennsylvania	Resident	1989- 1993	Surgery Resident
University of Texas M.D. Anderson Cancer Center, Houston, Texas	Fellowship	1993- 1996	Fellow, Surgical Oncology

A. POSITIONS AND HONORS

Positions

- 1996 - 1999 Assistant Professor of Surgery, Tulane University Medical Center, New Orleans, LA.
 1998 - 1999 Assistant Dean of Student Affairs, Tulane University School of Medicine, New Orleans, LA.
 1999 - 2001 Assistant Professor of Surgery, University of Tennessee Health Science Center, Department of Surgery, Memphis, TN
 2001 - 2005 Assistant Dean for Academic and Faculty Affairs, University of Tennessee Health Science Center, Memphis, TN
 2001 - 2006 Associate Professor of Surgery, University of Tennessee Health Science Center
 2006 - Present Professor and Chairman, Department of Surgery, Meharry Medical College, Nashville, TN

Other Experience and Professional Activities

- | | |
|--|--|
| American Association of Cancer Education | Society of Laparoendoscopic Surgeon |
| American Association for Cancer Research | Society of Surgical Oncology, Membership |
| American College of Surgeons – Fellow | Society for Black Academic Surgeons |
| American Hepato-Pancreato-Biliary Association | Southeastern Surgical Society |
| Association for Academic Surgery | Southern Medical Association |
| American Society of Breast Disease | Southeastern Surgical Congress – |
| Fellow Association for Surgical Education | Southwestern Medical Society |
| International College of Surgeons, United States Section | The Society of University Surgeons |
| International Society of Surgery | Western Surgical Association |
| International College of Surgeons | |
| M.D. Anderson Association | |
| National Medical Association | |

B. SELECTED PEER-REVIEWED PUBLICATIONS (IN CHRONOLOGICAL ORDER)

Peer Reviewed Books and Book Chapters

1. "Health Professions Education: A Bridge to Quality Institute of Medicine of the National Academies. **Beech DJ.** (*Journal of the National Medical Association*, September 2005 vol. 97:1308).
2. Ackerman T, Acton R, Austin J, Mack B, **Beech DJ**, Beenken S, Bland K, Chichakli R, Ellis N, Gingrich J, Grubbs E, Ludwig K, Mason R, Nabell L, Weiman D, Yelland J. "Inherited Cancer Syndromes" (Published by Springer-Verlag, New York 2003).
3. **Beech DJ.** "First, Do No Harm". PublishAmerica July 2003.
4. **Beech DJ.** "Life's Maze" Publications poetry.com
5. Elizabeth Speck, **Beech DJ.** The Importance of Breast Self-Exam"(Physician Q and A, Magazine, March 2003).

6. **Beech DJ**, Brown K. Closing The Gap. American Family Health Magazine, July/August 2003.
7. **Beech DJ**, Pollock R. Soft Tissue Sarcoma. Reconstructive Plastic Surgery for Cancer. ed. Kroll S. Mosby-Year Book, Inc., Philadelphia, PA., 1996.
8. Buckman RJ, Badellino M, **Beech DJ**. Special Problems in Abdominal Trauma. General Surgery, ed. WP Ritchie Jr., Glen Steele Jr., Richard Dean. J.B.Lippincott Company, Philadelphia, Pennsylvania. 1995.
9. **Beech DJ**, Lowy A. Oncologic Emergencies. MD Anderson Surgical Oncology Handbook. ed Berger D, Feig B, Fuhman G. Little, Brown, and Company Publishers, Boston, Mass. pg. 369-391, 1994.

Peer Reviewed Journal Articles (for a total of 59)

1. **Beech DJ**. Soft Tissue Sarcoma. J La State Med Soc. 1999 Jan; 151(1):33-41.
2. Madan AK, Yu K, **Beech DJ**. Alcohol and Drug Use in Victims of Life-Threatening Trauma. The Journal of Trauma, 47:3, September, 1999.
3. Madan AK, Pang Y, Wilkiemeyer MB, Yu D, **Beech DJ**. Increased Hyaluronidase Expression in More Aggressive Prostate Adenocarcinoma. Oncology Reports 1999 Nov; 6(6):1431-1433
4. Madan AK, **Beech DJ**, Yu K, Dhurandhar N, Cullinane C, Pang Y. Association of Hyaluronidase and Breast Adenocarcinoma Invasiveness. Oncology Reports 6:607-609, 1999
5. **Beech DJ**: Correlation of Alcohol Intoxication with Life-Threatening Assaults. Epikrisis, 10(2) pg 4, Summer, 1999.
6. Pontius A, Lund K, Zhang JW, **Beech DJ**. Metastatic Colorectal Cancer. Contemporary Surgery, October 1999; 55(4):212-216.
7. Aliabadi-Wahle S, Ebersole M, Choe EU, **Beech DJ**. Training in Clinical Breast Examination as Part of a General Surgery Core Curriculum. Journal of Cancer Education 2000, 15(1):10-13.
8. Godin DA, Fitzpatrick PC, Scandurro AB, Belafsky PC, Woodworth BA, Amedee RG, **Beech DJ**, Beckman BS. PH20: a novel tumor marker for laryngeal cancer. Arch Otolaryngology Head Neck Surg. 2000, Mar; 126(3):402
9. UyBarreta V, Mikesh C, Simmons B, **Beech DJ**. Atypical Presentation of Hepatocellular Carcinoma. The Southern Medical Journal, Vol 98, No. 5, May, 2000, pp 516-19.
10. Madan AK, Barden CB, Beech B, Fay K, Sintich M, **Beech DJ**. Socioeconomic Factors, Not Ethnicity, Predict Breast Self Examination. The Breast Journal. 6(4), 2000:263-266
11. Beech BM, Myers L, **Beech DJ**. Human Immunodeficiency Syndrome and Hepatitis B and C Infections Among Homeless Adolescents. (Seminars of Pediatric Infectious Diseases 2003 Jan. 14(1):12-9).
12. Speck E, **Beech DJ**. Diffuse Small Bowel Diverticulosis: Case Report and Review of Literature. Surgical Rounds. May 2003; 235-237.
13. **Beech DJ**, Long, A, Long, W. Dermatofibrosarcoma Protuberans and Breast Cancer: Genetic Link or Coincidental Association? Am Surg. June 2004; 543-545.
14. **Beech DJ**, Harb W, Reed J. Nodular Melanoma in the Face: A Rare Finding in African Americans. The American Surgeon. April 2004; 294-297.
15. **Beech DJ**, Hunter C. Ectopic Breast Tissue of The Axilla. Surgical Rounds. August 2003; 390-392
16. Madan AK, Barden CB, Beech B, Kelly F, Sintich M, **Beech, DJ**. Multivariate Analysis of Factors Associated with Smoking Cessation in Women. J La State Med Soc. March/April 2005; 112-115
17. Roth JA, **Beech DJ**, Putnam JM Jr., Pollock RE, Patel SR, Fidler IJ, Benjamin RS. Treatment of the patient with lung metastases. Curr Probl Surg. 1996 Nov; 33(11):881-952.
18. Madan A, **Beech DJ**. Laparoscopic revision of bariatric surgery. (Video submitted to American College of Surgeons annual meeting) October 2003.
19. Al-Juburi A, Granger S, Barnes J, Voeller G, **Beech DJ**, Amiri H, Abell T. Laparoscopy Shortens Length of Stay in Patients With Gastric Electrical Stimulators. Journal of the Society of Laparoendoscopic Surgeons July/September 2005; 9(3):305-310.
20. Mitchell S, Lachica R, Randall MB, **Beech DJ**. Paget's Disease of the breast areola mimicking cutaneous melanoma. The Breast Journal 2006 May-June; 12(3):233-236.

Ongoing Research Support

THE UTILITY OF XELODA® + IRESSA WITH EXTERNAL BEAM RADIATION AS ADJUVANT THERAPY FOR ADENOCARCINOMA OF THE RECTUM.

Sponsored by: Roche Pharmaceuticals 01/04 – present (\$78,000)



Vanderbilt University Medical Center

Vanderbilt Epidemiology Center

1215 21st Avenue South
Suite 6000 Medical Center East
Nashville, TN 37232-8300
phone (615) 936-1010
fax (615) 936-1269

Flora A. M. Ukoli, MBBS.,DPH.,MPH.
(Clinical Epidemiologist)
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37211


RE: Project Title: Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors

I have received and read a copy of this proposal and I am willing to participate as a co-investigator on this project. The study is designed to compare the effects of two forms of lycopene supplements on prostate cancer progression among men with biochemical failure. My contribution will include coordinating research activities across the departments at Vanderbilt, overseeing IRB and administrative activities, and supervising recruitment of participants and collection of data.

I will provide expertise in the design of the study, including strategies for participant retention. With my experience with dietary interventions and clinical trials I will also be involved in developing the safety and monitoring plans for this study. I plan to be involved in data analysis, interpretation and manuscript preparation.

Please keep me informed on the progress of the proposal and I look forward to working with you on this project.

Sincerely


Jay H. Fowke, Ph.D., MPH.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE		
Jay H. Fowke, Ph.D., MPH, M.S.	Assistant Professor of General & Internal Medicine		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Clark University, Worcester, MA	B.A.	1987	Biology
University of Michigan, Ann Arbor, MI	M.S.	1990	Neuroscience
State University of New York, Albany, NY	M.P.H.	1994	Epidemiology
University of Massachusetts, Amherst, MA	Ph.D.	2000	Epidemiology

Professional Experience

1990 - 1993	Research Assistant, Dept. of Environmental and Genetic Toxicology, New York State Department of Health, Albany, NY
1993	Research Assistant, Dept. of Environmental Health, State University of New York, Albany,
1994 - 1995	Research Assistant, Dept. of Epidemiology and Biostatistics, University of Massachusetts, Amherst, MA
1995-1997	Data Analyst, Dept. of Family and Occupational Medicine, University of Massachusetts Medical Center, Worcester, MA
1995 - 1999	Data Analyst, Dept. of Preventive and Behavioral Medicine, University of Massachusetts Medical Center, Worcester, MA
1998 - 1999	Project Coordinator, Dept. of Preventive and Behavioral Medicine, University of Massachusetts Medical Center, Worcester, MA
2000 - 2001	Research Assistant Professor, Dept. of Biostatistics and Epidemiology, University of South Carolina, SC
2001 - present	Assistant Professor, Dept. of General and Internal Medicine, Vanderbilt University, Nashville, TN

Awards and Organizations

Outstanding Student of the Year, University of Massachusetts School of Public Health

Society of Epidemiologic Research

2000 American Society of Preventive Oncology

2000 American Association of Cancer Research (Associate Member)

2002 American Association of Cancer Research (AACR) (Full Member)

2002 AACR Molecular Epidemiology Group

2004 NCI – Advanced Training Institute in Behavioral Theory – competitively selected to attend 8-day training workshop (San Diego) in behavior theory

Publications

1. DeCaprio, A.P., **Fowke J.H.** Limited and selective adduction of carboxyl-terminal lysines in the high molecular weight neurofilament proteins by 2,5-hexanedione *in vitro*. Brain Research, 586: 219-228, 1992.
2. DeCaprio, A.P., Spink, D.C., Chen, X., **Fowke, J.H.**, Zhu, M. Bank, S. Characterization of isothiocyanates, thioureas, and other lysine adduction products in carbon disulfide-treated peptides and protein. Chemical Research in Toxicology, 5: 469-504, 1992.
3. Richardson, R., Moore, T.B., Kayali, U.S., **Fowke, J.H.**, Randall, J.C. Inhibition of hen brain acetylcholinesterase and neurotoxic esterase by chlorpyrifos *in vivo* and kinetics of inhibition by Chlorpyrifos Oxon *in vitro*: Application to assessment of neuropathic risk. Fundamental and Applied Toxicology, 20: 273-279, 1993.

4. DeCaprio, A.P., Kinney, E.A., and **Fowke, J.H.** Regioselective binding of 2,5-hexandione to high-molecular-weight rat neurofilament proteins *in vitro*. *Toxicology and Applied Pharmacology*, 145: 211-217, 1997
5. Pransky, G., Long R., Hammer, K., Schulz, L.A., Himmelstein, J., **Fowke, J.H.** Screening for carpal tunnel syndrome in the workplace. *Journal of Occupational and Environmental Medicine*, 39: 727-733, 1997.
6. **Fowke J.H.**, Longcope C., Hebert, J.R. Brassica vegetable consumption increases the 2-hydroxyestrone/16alpha-hydroxyestrone ratio (2/16) in free-living postmenopausal women - *Cancer Epidemiology, Biomarkers, and Prevention*, 9: 773-779, 2000.
7. **Fowke J.H.** Longcope, C., Hebert J.R., Macronutrient intake and estrogen metabolism in healthy postmenopausal women. *Breast Cancer Research and Treatment*, 65(1) 1-10, 2001.
8. **Fowke J.H.**, Fahey, J.W., Stephenson, K., Hebert, J.R., Use of Urinary Isothiocyanate Excretion as a Biological Marker of Brassica Vegetable Consumption in Epidemiological Studies: Evaluating the Sources of Variability: *Public Health Nutrition*, 4(3): 837-846, 2001.
9. **Fowke, J.H.**, Hebert J.R. Fahey, J. W., Urinary Excretion of Dithiocarbamates and Self-Reported Cruciferous Vegetable Intake: Application of the 'Method of Triads' to a Food-Specific Biomarker. *Public Health Nutrition*. Dec. 5(6) 791-799, 2002.
10. **Fowke, J.H.**, Dai Q., Bradlow, HL, Shu X-O, Gao Y-T, Cheng J-R, Jin F, Zheng W. Urinary Estrogen Metabolites and Breast Cancer: differential pattern of risk found with pre-versus post-treatment collection. *Steroids*, 68(1): 65-72, 2003.
11. **Fowke, J.H.**, Chung, F-L, Jin, F., Dai, Q., Cai, Q., Conaway, C., Shu, X-O, Gao, Y-T., Zheng, W., Urinary Isothiocyanate Levels, *Brassica*, and Human Breast Cancer. *Cancer Research*. 63(14): 3980-3986, 2003.
12. **Fowke, J.H.**, Chung, F-L., Shu, X-O., Qi, D., Shintani, A., Conaway, C., Cai, Q., Gao, Y-T., Zheng, W. Associations of urinary isothiocyanate excretion, Brassica consumption, and genetic polymorphisms among women living in Shanghai, China. *Cancer Epidemiology, Biomarkers, and Prevention*, 12(12):1536-1540, 2003.
13. Matthews, C., **Fowke, J.H.**, Shu X-O, Gao Y-T, Cheng J-R, Jin F, Zheng W, (2004) Physical activity, body size, and estrogen metabolism in women. *Cancer Causes and Controls*, 15, 473-481, 2004.
14. **Fowke, J.H.**, Xiao-Ou Shu, Qi Dai, Qiuyin Cai, Wei Zheng Oral contraceptives and breast cancer risk: modification by NQO1 genetic polymorphisms, *Cancer Epidemiology, Biomarkers, and Prevention*, 13(8), 1308-1315, 2004.
15. **Fowke, J.H.**, Schlundt, D.G., Gong, Y., Jin, F. Shu, X. Wen, W. Liu, D. Gao, Y. Zheng, W. Impact of Season of Food Frequency Questionnaire administration on Dietary Reporting, *Annals of Epidemiology*, 14(10), 778-785, 2004.
16. **Fowke, JH**, Morrow J. Motley, S. Bostick, R.M. Ness, R. Brassica Vegetable Consumption Reduces Urinary F2-isoprostane Levels, a Biomarker of Systemic Oxidative Stress, *Carcinogenesis*, *in press*.
17. **Fowke, JH**, Schlundt, D., Signorello, L., Ukoli, F., Blot, W. Prostate cancer screening among low-income African-American and Caucasian men, *Urologic Oncology: Seminars and Original Investigations*, *in press*.

Free Communications / Posters:

1. **Fowke J.H.** Changes in Breast Milk PCB levels in relation to environmental exposure. Presentation to the Akwesasne Indian Tribe, Messena, NY 1993
2. **Fowke, J.H.**, Brix, K. Does breastfeeding change the PCB body burden. State University of New York at Albany Student Presentation Session 1993
3. Matthews, C. **Fowke, J.H.**, Hebert, J.R. Physical activity and estrogen metabolism in postmenopausal women. American College of Sports Medicine (New England chapter), Providence RI. 1999.

4. **Fowke, J.H.** Brassica vegetables and cancer risk: Current understanding and future outcomes for research studies. University of Massachusetts Medical Center, Breast Cancer Think-Tank 1999
5. Culp, A., Modayil, M., **Fowke J.H.** Psychosocial predictors of recruitment into breast cancer research studies. University of South Carolina School of Medicine, Columbia, SC, 2001.
6. **Fowke, J.H.**, Dai Qi, Bradlow, HL, Shu X-O, Gao Y-T, Cheng J-R, Jin F, Zheng W. Urinary estrogen metabolites and breast cancer in the Shanghai Breast Cancer Study. American Association of Cancer Research, 2002.
7. Harris, P.A., Fuller, R.E., and **Fowke, J.H.** A Data Collection Tool for use in Nutritional Assessment Studies. General Clinical Research Centers Conference, 2002.
8. **Fowke J.H.** The Estrogen-Androgen Balance Hypothesis and Prostate Cancer. Presentation to the Workshop on Prostate Cancer Research. Vanderbilt University, 2002
9. **Fowke, J.H.** Xiao-Ou Shu, Qi Dai, Qiuyin Cai, Wei Zheng. Oral Contraceptives, NQO1 Genotypes, and Breast Cancer. SNPs, Haplotypes, and Molecular Epidemiology Conference, 2003
10. **Fowke, J.H.**, Xiao-Ou Shu, Qi Dai, Qiuyin Cai, Wei Zheng Oral contraceptives and breast cancer risk: modification by NQO1 genetic polymorphisms, Minisymposium presentation at the American Association of Cancer Research, 2004.
11. **Fowke, J.H.** Morrow, J., Motley, S., Bostick R., Ness, R. Effects of Brassica on F2-isoprostanes. Plenary session presentation at the American Society of Preventive Oncology, 2005.

Current Research Support

RO1 CA70867 (Zheng, W)

09/17/96-05/31/08

Co-I

NIH: Cancer Risk Reduction and Diet: A Cohort Study of Women (Shanghai Women's Health Study)

To evaluate etiologic factors for cancer and other chronic diseases in a population-based prospective cohort study of 75,000 adult women. Dr. Fowke is responsible for analysis of diet-biomarker and diet-cancer relationships.

RO1 CA92447 (Blot, W)

9/28/01 to 8/31/06

Co-I

NIH: Southern Communities Cohort Study

A multi-racial cohort study investigating the role of racial disparities in cancer or other diseases. Dr. Fowke contributes to dietary assessment validation, protocol development, and evaluation of biomarkers of dietary intake and cancer risk.

P20 OMD000177 (Dittis, R.)

10/1/03-9/30/08

Co-I

NCMHHD Project EXPORT

This is the Meharry-Vanderbilt Center grant to expand health disparities research and build infrastructure at Meharry Medical School. Dr. Fowke serves as a collaborator and mentor in the fields of nutritional epidemiology, molecular epidemiology, prostate cancer epidemiology, and dietary intervention.

04B109 (Fowke, JH) – approved for funding

01/31/05 – 12/31/06

PI

AICR: Effects of Brassica or Indole-3-carbinol on Prostatectomy Patients with PSA Recurrence

This is a pilot randomized, placebo-controlled diet and dietary supplement intervention to determine the feasibility of Brassica consumption or Brassica phytochemicals use as adjuvant therapy among prostate cancer patients with PSA recurrence.

Department of Biostatistics

VANDERBILT



School of Medicine

October 27, 2006

Flora A. M. Ukoli, MBBS, DPH, MPH
Associate Professor, Department of Surgery
Meharry Medical College
1005 Dr. D.B. Todd Jr. Blvd.
Nashville, TN 37208-3599

Dear Dr. Ukoli,

It is with pleasure that I write this letter in support of your grant entitled "Lycopene supplementation in the complementary management of biochemical failure: A phase II randomized trial for prostate cancer survivors". I am looking forward to working with you, specifically in examining the differences in PSA trajectories over time; these types of mixed models are an area of interest to me and these methods will allow us to describe changes in PSA that can have important clinical implications for patients. I am more than happy to provide you with help in both experimental design and analyses. I have also attached a sample size calculation based on the information you supplied.

Sincerely,

Bonnie Laffleur PhD
Assistant Professor

An equal opportunity, affirmative action employer

VANDERBILT UNIVERSITY
1161 21st Ave. South, S-2323 MCN
Nashville, Tennessee 37232-2168

biostat.mc.vanderbilt.edu
tel 615.322.2001
fax 615.343.4924

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES**

NAME	POSITION TITLE		
Bonnie J. LaFleur	Assistant Professor, Department of		
eRA COMMONS USER NAME	Biostatistics, Vanderbilt University Medical		
bonnie lafleur	Center		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of California, San Diego	B.A.	1990	Sociology
San Diego State University	M.P.H.	1995	Biometry
University of Colorado Health Sciences Center	Ph.D.	1999	Biometrics

A. Positions and Honors. EMPLOYMENT HISTORY:

1990 - 1991 Research Associate, San Diego State University, Center for Behavioral Epidemiology.
1991 - 1992 Staff Research Associate, UCSD Medical Center, Department of Pulmonary Rehabilitation.
1992 - 1998 Biostatistician, Naval Health Research Center, Information Systems and Operations Research Department and Health Sciences and Epidemiology Department
1996 Statistical Consultant, State of Colorado, Department of Health Care Policy and Financing.
1995 - 1998 Research Assistant, University of Colorado Health Sciences Center, Department of Preventive Medicine and Biometrics.
1997 - 1998 Biostatistician, AMC Cancer Research Center, Department of Research Methodology and Biometrics.
1999 - 2001 Director of Biostatistics, National Children's Medical Center, Research Center.

FACULTY APPOINTMENTS:

2003- Assistant Professor, Vanderbilt University, Department of Biostatistics
2002- Adjunct Assistant Professor, Meharry Medical College, Department of Public Health Practice
2001 - Assistant Professor, Vanderbilt University, Department of Preventive Medicine
1999 - 2001 Assistant Research Professor, The George Washington University, Department of Epidemiology and Biostatistics.

GRANTS AND AWARDS:

1998-1999 Research Fellow – Center for Disease Control and Prevention, The National Center for Health Statistics, Office of Analysis, Epidemiology and Health Promotion.
1997 Strother Walker Award for outstanding PhD student in biometrics

B. Selected peer-reviewed publications (37 of 50 publications in chronological order).

Khatua S, Peterson KM, Brown KM, Lawlor C, Santi MR, **LaFleur BJ**, Dressman D, Stephan DA, Talbot TR, Bredenberg HK, Smith M, **LaFleur BJ**, Boyd A, Edwards KM (2003) Focal and generalized folliculitis following smallpox vaccination among vaccinia-naïve recipients. *JAMA*, 289(24), 3290-4.
Wong EC, Schreiber S, Criss VR, **LaFleur BJ**, Rais-Bahrami K, Short B, Luban NL (2004) Feasibility of red blood cell transfusion through small bore central venous catheters used in neonates. *Pediatric Critical Care Medicine*, 5(1), 69-74.
Deane NG, Lee H, Hamaamen J, Ruley A, Washington MK, **LaFleur BJ**, Thregeirsson SS, Price R, Beauchamp RD (2004) Enhanced tumor formation in cyclin d1 x transforming growth factor betall double transgenic mice with characterization by magnetic resonance imaging. *Cancer Research*, 64(4), 1315-1322.
Talbot TR, Ziel E, Doersam JK, **LaFleur BJ**, Tollefson S, Edwards KM (2004) Risk of vaccinia transfer to the hands of vaccinated persons after smallpox immunization. *Clin Infect Dis*, 38(4), 536-41.

- Shuford MD, McDougall EM, Chang SS, **LaFleur BJ**, Smith JA Jr, Cookson MS (2004) Complications of contemporary radical nephrectomy: comparison of open vs. laparoscopic approach. *Urol Oncol*, 22(2), 121-6.
- Amiri KI, Horton LW, **LaFleur BJ**, Sosman JA, Richmond A. (2004) Augmenting chemosensitivity of malignant melanoma tumors via proteasomeinhibition: implication for bortezomib (VELCADE, PS-341) as a therapeutic agent for malignant melanoma. *Cancer Research*, 64(14), 4912-8.
- Weinberg A, Wiznia AA, **LaFleur BJ**, Shah S, Levin MJ. (2004) Varicella-Zoster virus-specific cell-mediated immunity in HIV-infected children receiving highly active antiretroviral therapy. *Journal of Infectious Diseases*, 190(2), 267-70.
- Jones TF, Pavlin BI, **LaFleur BJ**, Ingram LA, Schaffner W. (2004) Restaurant inspection scores and foodborne disease. *Emerging Infectious Diseases Journal*. 10(4) 688-92.
- Richard C, Gao J, **LaFleur BJ**, Christman BW, Anderson J, Brown N, Reese J. (2004) Patency of the Preterm Fetal Ductus Arteriosus is Regulated by Endothelial Nitric Oxide Synthase and is Independent of Vasa Vasorum in the Mouse. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*.
- Poehling K, **LaFleur BJ**, Szilagyi PG, Edwards KM, Mitchel E, Barth R, Schwartz B, Griffin MR. (2004) Population-based Impact of Pneumococcal Conjugate Vaccine in Young Children. *Pediatrics*, 114:755-761.
- Mitchell SA, Brown KM, Henry MM, Mintz M, Catchpoole D, **LaFleur B**, Stephan DA. Inter-Platform Comparability Of Microarrays In Acute Lymphoblastic Leukemia. (2004). *BMC Genomics*, 5(1):71.
- Mintz MB, Sowers R, Brown KM, Hilmer SC, Mazza B, Huvos AG, Meyers PA, **LaFleur B**, McDonough WS, Henry MM, Ramsey KE, Antonescu CR, Chen W, Healey JH, Daluski A, Berens ME, Macdonald TJ, Gorlick R, Stephan DA. (2005). An Expression Signature Classifies Chemotherapy-Resistant Pediatric Osteosarcoma. *Cancer Research*, 5(5):1748-54.
- Weitkamp JH, Kallewaard NL, Bowen AL, **LaFleur BJ**, Greenberg HB, Crowe JE Jr. (2005). VH1-46 Is The Dominant Immunoglobulin Heavy Chain Gene Segment In Rotavirus-Specific Memory B Cells Expressing The Intestinal Homing Receptor Alpha4beta7. (2005). *Journal of Immunology*, 174(6):3454-60.
- Weitkamp JH, **LaFleur BJ**, Greenberg HB, Crowe JE Jr. (2005). Natural Evolution Of A Human Virus-Specific Antibody Gene Repertoire By Somatic Hypermutation Requires Both Hotspot-Directed And Randomly-Directed Processes. *Human Immunology*. 66(6):666-76.
- Mintz MB, Sowers R, Brown KM, Hilmer SC, Mazza B, Huvos AG, Meyers PA, **LaFleur B**, McDonough WS, Henry MM, Ramsey KE, Antonescu CR, Chen W, Healey JH, Daluski A, Berens ME, Macdonald TJ, Gorlick R, Stephan DA. (2005). An Expression Signature Classifies Chemotherapy-Resistant Pediatric Osteosarcoma. *Cancer Research*. 65(5):1748-54.
- Guthrie SO, Lynn C, **LaFleur BJ**, Donn SM, Walsh WF. (2005). A crossover analysis of mandatory minute ventilation compared to synchronized intermittent mandatory ventilation in neonates. *Journal of Perinatology*. 25(10):643-6.
- Dunckley T, Beach TG, Ramsey KE, Grover A, Mastroeni D, Walker DG, **LaFleur BJ**, Coon KD, Brown KM, Caselli R, Kukull W, Higdon R, McKeel D, Morris JC, Hulette C, Schmechel D, Reiman EM, Rogers J, Stephan DA. (2005). Gene expression correlates of neurofibrillary tangles in Alzheimer's disease. *Neurobiology of Aging*. [Epub ahead of print].
- Weinberg A, Wiznia AA, **LaFleur BJ**, Shah S, Levin MJ. (2006). Cytomegalovirus-specific cell-mediated immunity in HIV-infected children on HAART. *AIDS Research and Human Retroviruses*. 22(3):283-8.
- Weitkamp JH, **LaFleur BJ**, Crowe JE. (2006). Rotavirus-specific CD5⁺ B cells in young children exhibit a distinct antibody repertoire compared with CD5⁺ B cells. *Human Immunology*. 67(1-2):33-42.
- Bowen AL, Cuixia T, **LaFleur BJ**, Crowe JE. (2006). Transcriptional control of activation-induced cytidine deaminase and error-prone DNA polymerases is functionally mature in the B cells of infants at birth. *Human Immunology*. 67(1-2):43-6.
- Poehling KA, Szilagyi P, Grijalva CG, **LaFleur B**, Ed Mitchel E, Barth R, Nuorti PJ, Griffin MR. (2006). Reduction of otitis media, frequent otitis media and pressure equalizing tube insertions in children since heptavalent pneumococcal conjugate vaccine introduction. *JAMA* (submitted).

Leys CM, Nomura S, **LaFleur BJ**, Ferrone S, Kaminishi M, Montgomery E, Goldenring JR. (2006). Expression and Prognostic Significance of Prothymosin-alpha and ERp57 in Human Gastric Cancer. *Surgery*. (In press).

LaFleur BJ, Billheimer DD, Chen H. (2006). Likelihood-based evaluation of normalization methods. *Bioinformatics* (submitted – under review).

LaFleur BJ, Greevy RA. (2006). Introduction and Review of Permutation Tests in Clinical Child and Adolescent Psychology. (part 1 of a 2 part invited paper series submitted to the Journal of Clinical Child and Adolescent Psychology).

Dunckley T, Beach TG, Ramsey KE, Grover A, Mastroeni D, Walker DG, **LaFleur BJ**, Coon KD, Brown KM, Caselli R, Kukull W, Higdon R, McKeel D, Morris JC, Hulette C, Schmechel D, Reiman EM, Rogers J, Stephan DA. (2005) Gene expression correlates of neurofibrillary tangles in Alzheimer's disease. *Neurobiol Aging*. Oct 18. [Epub ahead of print]

C. Research Support

(of 7: No Overlap.)

LaFleur, Bonnie **Active**

1. P20 MD00516-03 Dittus (PI) 9/30/03-08/31/07
NIH
“Project Export”
To build an infrastructure at Meharry Medical College to study health disparities among minorities.
Role: Co-Investigator
2. U01 CA84239-08 Coffey (PI) 09/15/04-03/31/09
NCI
“Prevention & Metastasis: Final Frontiers in Colon Cancer”
To study gastrointestinal cancer research using mouse models (part of MMH).
Role: Co-Investigator
3. P30 CA068485-11 DuBois (PI) 09/28/04-08/31/09
NCI
“Cancer Center Support Grant”
To expand the research base at the Vanderbilt-Ingram Cancer Center.
Role: Co-Investigator
4. R01 CA107493-02 Sosman (PI) 09/29/04-08/31/07
NCI
“Overcoming DC Defects in Cancer Patients with VEGF Trap”
To incorporate biochemical markers as endpoints in a clinical trial.
Role: Co-Investigator
5. R21 ES013730-01A1 Aschner (PI) 06/08/06-05/31/08
NIEHS
“Brain Manganese Deposition in High-Risk Neonates”
Role: Co-Investigator
6. P01 1R21 CA040035-18A1 Mundy (PI) 09/01/06-08/31/11
NCI
“Effect of Tumors on the Skeleton”
Role: Co-Investigator
7. R21 CA123061-01 Means (PI) 07/01/06-06/30/08
NCI
“The Role of EGFR Signaling in Progression of Kras-Induced Pancreatic Tumors”
Role: Co-Investigator

Completed

None



December 12, 2007

Flora A. M. Ukoli, MBBS, DPH, MPH.
Clinical Epidemiologist
Department of Surgery
Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, Tennessee 37211

RE: Project Titled: "Lycopene supplementation in the complementary management of Biochemical failure:
A phase II randomized trial for prostate cancer survivors"

Dear Dr. Ukoli:

I have received and read a copy of this proposal and I am willing to participate as an investigator on the project. The study is designed to assess the adherence of a lycopene-rich diet and to evaluate the preventive effects of the diet on prostate cancer progression reduction. My contribution to the success of this project will include arranging for isoprostane assay and getting involved with data analysis and interpretation and I will also plan time to contribute to the development of reports and manuscripts.

Sincerely,

Jason D. Morrow, M.D.
Professor of Medicine and Pharmacology
Chief, Division of Clinical Pharmacology
Vanderbilt University School of Medicine
Nashville, TN 37232

JDM/dmg

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BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Photocopy this page or follow this format for each person.

NAME Morrow, Jason D., M.D.	POSITION TITLE <u>Professor of Medicine and Pharmacology</u>
---------------------------------------	---

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Vanderbilt University, Nashville, TN	B.S.	1979	Molecular Biology and Chemistry
Washington University, St. Louis, MO	M.D.	1983	Medicine

NOTE: The Biographical Sketch may not exceed four pages. Items A and B may not exceed two of the four-page limit.

- A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

Professional Experience

1983 - 1986 Resident in Medicine, Vanderbilt University Medical Center
1986 - 1987 Clinical Fellowship, Infectious Diseases, Barnes Hospital, Washington University
1987 - 1988 Hugh J. Morgan Chief Medical Resident, Vanderbilt University Medical Center
1988 - 1991 Fellow in Clinical Pharmacology, Vanderbilt University Medical Center
1991 - 1994 Senior Research Fellow, Vanderbilt University Medical Center
1990 - present Staff Physician, VA Medical Center, Nashville, TN
1992 - present Director, Eicosanoid Core Laboratory, Division of Clinical Pharmacology
1994 - 1995 Assistant Professor of Medicine and Pharmacology, Vanderbilt University School of Med
1995 - 1999 Associate Professor of Medicine and Pharmacology, Vanderbilt University School of Med.
1997 - 2003 Director, Medical Scholars Research Training Program, Vanderbilt Univ. School of Med.
1998 - 2003 Director, Residents Research Program, Vanderbilt University School of Medicine
1999 - present F. Tremaine Billings Prof. of Medicine and Pharmacology, Vanderbilt Univ. School of Med
2000 - present Director, Research Center for Pharmacology, Vanderbilt University School of Medicine
2002 - 2003 Chairman, Medical Biochemistry Study Section, NIH
2002 - present Editorial Board, *Journal of Biological Chemistry*
2003 - present Associate Dean for Physician-Scientist Development, Vanderbilt University School of Med.
2003 - present Editorial Board, *Arteriosclerosis, Thrombosis and Vascular Biology*

Awards

1990 - 1991 NIH Physician Scientist Award
1990 - 1991 Boehringer-Ingelheim Centennial Fellow in Clinical Pharmacology
1990 - 1991 Burroughs Wellcome Fellow in Clinical Pharmacology (declined)
1991 - 1995 Howard Hughes Medical Institute Physician Research Fellow
1992 - 1995 International Life Sciences Institute Career Development Award
1996 Grant Liddle Research Award, Vanderbilt University
1999 American Society for Clinical Investigation
1999 - 2004 Burroughs Wellcome Fund Clinical Scientist Award in Translational Research

- B. Selected peer-reviewed publications (in chronological order).** Do not include publications submitted or in preparation.

- Morrow JD, Harris TM, Roberts LJ. Non-cyclooxygenase oxidative formation of a series of novel prostaglandins: analytical ramifications for measurement of eicosanoids. *Analyt. Biochem.* 185:1-10, 1990.
- Morrow JD, Hill KE, Burk RF, Badr KF, Nammour T, Roberts LJ. A series of prostaglandin F₂-like compounds are produced *in vivo* in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc. Natl. Acad. Sci. U.S.A.* 87:9383-7, 1990.
- Morrow JD, Awad J, Oates JA, Roberts LJ. Identification of skin as a major site of PGD₂ release following oral administration of niacin in humans. *J. Invest. Dermatol.* 98:812-5, 1992.

4. Morrow JD, Awad JA, Boss HJ, Blair IA, Roberts LJ. Non-cyclooxygenase-derived prostanoids (F₂-isoprostanes) are formed in situ on phospholipids. *Proc. Natl. Acad. Sci. U.S.A.* 89:10721-5, 1992.
5. Morrow JD, Awad JA, Kato T, Takahashi K, Badr KF, Roberts LJ, Burk RF. Formation of novel non-cyclooxygenase prostanoids (F₂-isoprostanes) in carbon tetrachloride hepatotoxicity, an animal model of lipid peroxidation. *J. Clin. Invest.* 90:2502-7, 1992.
6. Morrow JD, Minton TA, Badr KF, Roberts LJ. Evidence that the F₂-isoprostane, 8-epi-prostaglandin F_{2α}, is formed *in vivo*. *Biochem. Biophys. Acta* 1210:244-8, 1994.
7. Morrow JD, Minton TA, Zackert WE, Awad JA, Campbell MD, Mukundan C, Blair IA, Badr KF, Roberts LJ. Free radical induced generation of isoprostanes *in vivo*: Evidence for the formation of D-ring and E-ring isoprostanes. *J. Biol. Chem.* 269:4317-26, 1994.
8. Chaudhary AK, Nokubo M, Reddy GR, Yeola SN, Morrow JD, Blair IA, Marnett LJ. Detection of endogenous malondialdehyde-deoxyguanosine adducts in human liver. *Science* 265:1580-1, 1994.
9. Morrow JD, Frei B, Gaziano JM, Lynch SM, Shyr Y, Oates JA, Roberts LJ. Increase in circulating products of lipid peroxidation (F₂-isoprostanes) in smokers. *N. Engl. J. Med.* 322:1198-1203, 1995.
10. Landino LM, Crews BC, Morrow JD, Marnett LJ. Peroxynitrite, the coupling product of nitric oxide and superoxide, activates prostaglandin biosynthesis. *Proc. Natl. Acad. Sci. U.S.A.* 93:15069-74, 1996.
11. May JM, Qu ZC, Morrow JD. Interaction of ascorbate and alpha-tocopherol in resealed human erythrocyte ghosts. Transmembrane electron transfer and protection from lipid peroxidation. *J. Biol. Chem.* 271:10577-82, 1996.
12. Morrow JD, Wu A, Zackert WE, Roberts LJ. Non-enzymatic free radical catalyzed generation of thromboxane-like compounds (isothromboxanes) *in vivo*. *J. Biol. Chem.* 271:23185-90, 1996.
13. Morrow JD, Moore KP, Zackert WE, Oates JA, Roberts LJ. Identification of the major urinary metabolite of the F₂-isoprostane 8-iso-prostaglandin F_{2α} in humans. *J. Biol. Chem.* 271:20617-20, 1996.
14. Coffey RJ, Hawkey CJ, Damstrup L, Graves-Deal R, Daniel VC, Dempsey PJ, Chinery R, Kirkland SC, DuBois RN, Jetton TL, Morrow JD. Epidermal growth factor receptor activation induces nuclear targeting of cyclooxygenase-2, basolateral release of prostaglandins, and mitogenesis in polarizing colon cancer cells. *Proc. Natl. Acad. Sci. U.S.A.* 94:657-62, 1997.
15. Roberts LJ, Montine TJ, Markesbery WR, Tapper AR, Chemtob S, Dettbarn WD, Morrow JD. Formation of isoprostane-like compounds (neuroprostanes) *in vivo* from docosahexaenoic acid. *J. Biol. Chem.* 273:13605-12, 1998.
16. Chinery R, Coffey RJ, Graves-Deal R, Sanchez SC, Oates JA, Morrow JD. Prostaglandin J₂ and 15-deoxy-Δ^{12,14}-prostaglandin J₂ induce proliferation of cyclooxygenase-depleted colorectal cancer cells. *Cancer Res.* 59:2739-46, 1999.
17. Montine TJ, Beal MF, Roberts LJ, Morrow JD. Increased CSF F₂-isoprostane concentration in probably AD. *Neurology* 52:562-5, 1999.
18. Reich EE, Zackert WE, Brame CJ, Chen Y, Roberts LJ, Hachey DL, Montine TJ, and Morrow JD. Formation of novel D-ring and E-ring isoprostane-like compounds (D₄/E₄-neuroprostanes) *in vivo* from docosahexaenoic acid. *Biochemistry* 39:2376-83, 2000.
19. Marnett LJ, Wright TL, Crews BC, Tannenbaum SR, Morrow JD. Regulation of prostaglandin biosynthesis by nitric oxide is revealed by targeted deletion of inducible nitric-oxide synthase. *J. Biol. Chem.* 275:13427-40, 2000.
20. Levine ML, Wang Y, Padayatty S, Morrow JD. A new recommended dietary allowance of vitamin C for young healthy women. *Proc. Natl. Acad. Sci. U.S.A.* 98:5277-80, 2001.

21. Nieman DC, Hensen DA, McAnulty SR, McAnulty L, Swick NS, Utter AC, Vinci DM, Opeliela SJ, Morrow JD. Influence of vitamin C supplementation on oxidative and immune changes following an ultramarathon. *J. Appl. Physiol.* 92:1970-7, 2002.
 22. Fam SS, Murphey LJ, Terry ES, Zackert WE, Chen Y, Gao L, Pandalai S, Milne GL, Roberts LJ, Porter NA, Montine TJ, Morrow JD. Formation of highly reactive A-ring and J-ring isoprostane-like compounds (A₄/J₄-Neuroprostanes) from docosaheptaenoic acid. *J. Biol. Chem.* 277:36076-84, 2002.
 23. Hubatsch I, Mannervik B, Gao L, Roberts LJ, Chen Y, Morrow JD. The cyclopentenone product of lipid peroxidation, 15-A_{2t}-IsoP (8-iso-prostaglandin A₂) is efficiently conjugated with glutathione by human and rat glutathione transferase A4-4. *Chem. Res. Toxicol.* 15:1114-8, 2002.
 24. Montine TJ, Montine KS, Reich EE, Terry ES, Porter NA, Morrow JD. Comparison of the formation of different classes of isoprostanes and neuroprostanes in rat cerebral synaptosomes-effects of various antioxidants. *Biochem. Pharmacol.* 65:611-27, 2003.
 25. Gao L, Zackert WE, Hasford JJ, Danekis ME, Milne GL, Remmert C, Reese J, Yin H, Tai H-H, Dey SK, Porter NA, Morrow JD. Formation of Prostaglandins E₂ and D₂ via the isoprostane pathway: a mechanism for the generation of bioactive prostaglandins independent of the cyclooxygenase. *J. Biol. Chem.* 278:28479-28489, 2003.
- C. Research Support.

ONGOING

1P50 CA95103-01 (Coffey, RJ)
NIH/NCI (CA)
SPORE in GI Cancer

08/01/02 - 04/30/07

5M01 RR00095-43 (Wood)
NIH/NCRR (RR)

12/01/02 – 11/30/07

General Clinical Research Center - GCRC-Medical Scholars Program.
This is a training program for medical students in research.

Completed: (Selected from 2006 only)

5P50 GM15431-35 (Morrow, JD)
NIH/NIGMS

07/01/01 - 06/30/06

Research Center for Pharmacology and Drug Toxicology
The goal of this Center is to study the biology and pharmacology of eicosanoids

5R37 GM42056-14 (Roberts, LJ)
NIH/NIGMS

07/01/01 - 06/30/06

Structural Identification of Prostaglandin Conjugates

5P50 CA90949-02 (Carbone, DP)
NIH/NCI

06/28/01- 12/31/06

SPORE in Lung Cancer
Studies examine role of prostaglandins in lung cancer.

5R01 CA46413-15 (Coffey, RJ)
NIH/NCI

04/01/01 - 03/31/06

Role of EGF Receptor Ligands in Neoplasia
This study explores the role of growth factors and prostaglandin production in colon cancer cells.

Cookson

BIOGRAPHICAL SKETCH			
Provide the following information for the key personnel in the order listed for Form Page 2. Follow the sample format for each person. DO NOT EXCEED FOUR PAGES.			
NAME		POSITION TITLE	
Cookson, Michael S.		Assistant Professor of Urologic Surgery	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Oklahoma, Norman, OK	B.A.	1980-1984	Journalism
University of Oklahoma College of Medicine, Oklahoma City, OK	M.D.	1984-1988	Medicine

A. Positions and Honors.

Positions and Employment

1988-1989	General Surgery Internship, Dept.of Surgery, University of Texas at San Antonio
1989-1993	Urology Residency, Division of Urology, Department of Surgery, University of Texas at San Antonio
1993-1994	Chief Resident, Urology, Division of Urology, Department of Surgery, University of Texas at San Antonio
1994-1996	Urologic Oncology Fellowship, Memorial Sloan-Kettering Cancer Center, New York, New York
1996-1998	Chief of Urology and Staff Surgeon, Division of Urology, Department of Surgery, Lexington Veterans Administration Hospital, Kentucky
1996-1998	Assistant Professor of Surgery, Chief of Urologic Oncology, Division of Urology, University of Kentucky College of Medicine, Kentucky
1998-present	Assistant Professor, Department of Urologic Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee

Other Experience and Professional Memberships

1996-1998	Genitourinary Committee, Southwest Oncology Group(SWOG)
1996-1998	Member, Fayette County Medical Society
1996-1998	Member, Kentucky Medical Society
1996-1998	Member, Kentucky Urologic Association
1996-present	American Urological Association
1996-present	American Medical Association
1996-present	Society for Surgical Oncology
1996-present	Southeastern Section of the American Urological Association
1997-present	Publication Reviewer, Journal of Urology
1998-present	American Association of Clinical Urologists
1998-Present	Member, Eastern Cooperative Oncology Group (ECOG)
1998-present	Societe Internationale D'Urologie
1998-present	Publication Reviewer, Cancer
1998-present	Vanderbilt Urology Society
1999-present	Society of Urologic Oncology
2000-2002	AUA Research Council, Section Alternate Representative
2000-present	American College of Surgeons
2001-2004	Executive Committee, Society of Urologic Oncology
2002-2004	Journal of Urology, Specialty Society Editor
2002-2004	Society of Urologic Oncology

Honors

1980	Alpha Lambda Delta, National Freshman Honor Society, University of Oklahoma
1983	Golden Key National Honor Society, University of Oklahoma
1982-1984	Pi Eta Sigma, National Honor Society, University of Oklahoma
1980-1984	Honors Program, University of Oklahoma
1982	Scholarship Leadership Enrichment Program, University of Oklahoma

B. Selected peer-reviewed publications.

(Publications selected from 48 peer-reviewed publications)

1. HW Herr, MS Cookson and SM Soloway. Upper tract tumors in patients with primary bladder cancer followed for 15 years. *Journal of Urology* 156: 1286-1287, 1996.
2. EJ Feleppa, A Kalisz, JB Sokil-Melgar, FL Lizzi, T Liu, AL Rosado, MC Shao, WR Fair, Y Wang, MS Cookson, VE Reuter and WDW Heston. Typing of prostate tissue by ultrasonic spectrum analysis. *IEEE Transactions On Ultrasonics, Ferroelectrics and Frequency Control* 43: 609-619, 1996
3. MS Cookson, PC Sogani, P Russo, J Sheinfeld, H Herr, G Dalbagni, VE Reuter, CB Begg and WR Fair. Pathological staging and biochemical recurrence after neoadjuvant androgen deprivation therapy in combination with radical prostatectomy in clinically localized prostate cancer: results of a phase II study. *British Journal of Urology*. 79(3): 432-438, 1997.
4. MS Cookson, VE Reuter, I Linkov, WR Fair. Glutathione S-Transferase Pi (GST-) expression by immunohistochemistry in benign and malignant prostate tissue. *Journal of Urology (Investigative Section)* 157: 673-676, 1997.
5. MS Cookson, NE Fleshner, SM Soloway, WR Fair. Prognostic significance of prostate-specific antigen in stage T1c prostate cancer treated by radical prostatectomy. *Urology*. 49(6):887-93, 1997.
6. NE Flesher, MS Cookson, S Soloway and WR Fair. Repeat transrectal ultrasound guided prostate biopsy: a strategy to improve the reliability of needle biopsy grading in patients with well-differentiated prostate cancer. *Urology* 52(4):659-62, 1998.
7. MS Cookson. Androgen deprivation therapy prior to radical prostatectomy and radiation therapy for clinically localized (Stage T1/T2) prostate cancer: status and potential pitfalls. *Molecular Urology* 1:191-198, 1997.
8. MS Cookson, PC Sogani, P Russo, J Sheinfeld, H Herr, G Dalbagni, VE Reuter, CB Begg and WR Fair. Pathological staging and biochemical recurrence after neoadjuvant androgen deprivation therapy in combination with radical prostatectomy in clinically localized prostate cancer: results of a phase II study. *British Journal of Urology*. 79(3):432-438, 1997.
9. MS Cookson. Update on Transrectal Ultrasound-Guided Needle Biospy of the Prostate. *Molecular Urology* 4 (3): 93-97, 2000.
10. DJ Grossklaus, SB Shappell, S Gautam, JA Smith, Jr. and MS Cookson. Ratio of Free-to-total Prostate Specific Antigen Correlates with Tumor Volume in Patients with Increased Prostate Specific Antigen. *Journal of Urology* 165: 455-458, 2001.
11. MS Cookson. Prostate Cancer: Screening and Early Detection. *Cancer Control* 8(2): 133-140, 2001.
12. SS Chang G Albert, N Wells, JA Smith, Jr. and MS Cookson. Intrarectal Lidocaine During Transrectal Prostate Biopsy. *Journal of Urology* 166: 2178-2180, 2001.

13. PK Pietrow, DJ Parekh, JA Smith, Jr., Y Shyr and MS Cookson. Health Related Quality of Life Assessment Following Radical Prostatectomy in Men with Prostate Specific Antigen-Only Recurrence. Journal of Urology 166: 2286-2290, 2001.
14. DJ Grossklaus, CS Coffey, SB Shappell, GS Jack, and MS Cookson. Prediction of Tumor Volume and Pathologic Stage in Radical Prostatectomy Specimens is not Enhanced by Increasing the Number of Prostate Needle Biopsy Cores. British Journal of Urology International 88(7): 722-726, 2001.
15. DJ Grossklaus, CS Coffey, SB Shappell, GS Jack, SS Chang and MS Cookson. Percent of Cancer in Biopsy Set Predicts Pathologic Findings After Radical Prostatectomy. Journal of Urology 167: 2032-2036, 2002.

C. Research Support

Ongoing Research Support

2 CA37429 Cookson (PI)

6/1/00 - 5/31/12

SWOG through NIH

Selenium and Vitamin E Cancer Trial/(SELECT)

The goal of this study of to evaluate the effectiveness of vitamin therapy (Selenium and Vitamin E) on the prevention of prostate cancer.

Role: PI

UNIVERSITY OF MINNESOTA

Twin Cities Campus

*Department of Laboratory
Medicine & Pathology*

Medical School

*Mayo Mail Code 609
420 Delaware Street S.E.
Minneapolis, MN 55455
Phone: 612-624-5417
Fax: 612-273-6994
E-mail: gross@epi.umn.edu*

October 25, 2006

Flora A. M. Ukoli, MBBS, DPH, MPH.
Meharry Medical College
Department of Surgery
4th Floor Old Hospital Building
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville TN 37208

Dear Dr. Ukoli;

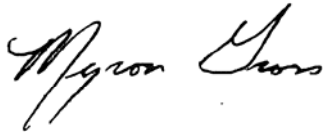
Re: Lycopene supplementation in the complementary management of PSA failure: A Phase II randomized trial for prostate cancer survivors.

I am interested in lycopene and its possible biological actions. Now several studies have indicated a possible protective role for lycopene and demonstrated a possible effect on the risk of prostate cancer. Your proposed project in the area of lycopene is very interesting. It addresses an important question in the field, appears feasible and will provide interesting new data.

I would be very happy to collaborate with you on the project. My laboratory has extensive experience with the measurement of carotenoids, including lycopene. We can measure readily the proposed samples from your study. I look forward to a productive and exciting research project. I will gladly help you with the proposed project and provide laboratory support for the proposed analysis in the carotenoid area.

Since this is an initial collaboration with our laboratory, we will provide these assays at a reduced cost on a one-time-only basis.

Thanks,



Myron Gross
Associate Professor
Department of Laboratory Medicine and Pathology
University of Minnesota

biographical sketch

NAME		POSITION TITLE	
Myron D. Gross, Ph.D.		Associate Professor	
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Minnesota, Minneapolis, MN	B.S.	1974	Animal Science
	M.S.	1977	Animal Science
	Ph.D.	1985	Nutrition/
			Biochemistry

RESEARCH AND PROFESSIONAL EXPERIENCE:

A. Professional Experience

- 1984-87 Endocrine Research Unit, Mayo Clinic, Rochester, MN: Research Fellowship, National Research Service Award
- 1987-90 University of Minnesota, Division of Epidemiology: Research Associate
- 1990-98 University of Minnesota, Division of Epidemiology: Assistant Professor
- 1998-99 University of Minnesota, Division of Epidemiology: Associate Professor
- 1998-present University of Minnesota: Director MEBRL and adjunct Associate Professor, Division of Epidemiology
- 1999-present University of Minnesota, Laboratory Medicine & Pathology: Associate Professor

B. Publications

1. Gross MD, Yu X, Hannan P, Prouty C, Jacobs DR. Lipid standardization of serum fat-soluble antioxidant concentrations: the YALTA study. *Am J Clin Nutr* 77:458-66, 2003.
2. Lee DH, Ha MH, Kim JR, Gross MD, Jacobs DR. Gamma-glutamyltransferase, alcohol, and blood pressure: A four year follow-up study. *Ann Epidemiol* 12:90-6, 2002.
3. Lee D-H, Ha M-H, Kim J-H, Christiani DC, Gross MD, Steffes M, Blomhoff R, Jacobs DR. Gamma-glutamyltransferase and type 2 diabetes-A 4 year follow up study. *Diabetologia*, In press, 2003.
4. Murtaugh MA, Jacobs DR, Yu X, Gross MD, Steffes M. Correlates of urinary albumin excretion in black and white young adults: the CARDIA Study. *American Journal of Epidemiology*, In Press, 2003.
5. Periera AM, Jacobs Jr DJ, Pins JJ, Raatz SK, Gross MD, Slavin JL, Seaquist ER. The Effect of Whole Grains on Insulin Sensitivity in Overweight Hyperinsulinemic Adults. *Am J Clin Nutr*, 75(5):848-855, 2002.
6. Arts ICW, Jacobs Jr. DR, Harnack LJ, Gross MD, Folsom AR. Dietary Catechins: Intake and Relation to Coronary Heart Disease Death Among Postmenopausal Women. *Epidemiology*, 12(6):668-675, 2001.
7. Comstock, George W., Burke A, Hoffman S, Norkus E, Gross M, Helzlsouer. The Repeatability of Serum Carotenoid, Retinoid, and Tocopherol Concentrations in Specimens of Bloods Collected 15 years Apart. *CEBP*, 10:65-68; 2001.
8. Deitz AC, Zheng W, Leff M, Gross M, Wen W-Q, Doll M, Xiao G, Folsom A, Hein D. N-Acetyltransferase-2 Genetic Polymorphism, Well-Done Meat Intake, and Breast Cancer Risk among Postmenopausal Women. *CEBP*, 9:905-910, 2000.
9. Kritchevsky S, Bush A, Pahor M, Gross M. Serum Carotenoids and Markers of Inflammation in Non-Smokers. *Am J Epi*, 152(11):1065-71; 2000.
10. Reich EE, Montine KS, Gross MD, Roberts II LJ, Swift LL, Morrow JD, Montine TJ. Interactions between Apolipoprotein E Gene and Dietary α -tocopherol Influence Cerebral Oxidative Damage in Aged Mice. *Journal of Neuroscience*, 21(6):5993-5999; 2001..
11. Comstock, George W., Burke A, Hoffman S, Norkus E, Gross M, Helzlsouer. The Repeatability of Serum Carotenoid, Retinoid, and Tocopherol Concentrations in Specimens of Bloods Collected 15 years Apart. *CEBP*, 10:65-68; 2001.

12. Kritchevsky S, Bush A, Pahor M, Gross M. Serum Carotenoids and Markers of Inflammation in Non-Smokers. Am J Epi, 152(11):1065-71; 2000.
13. Iribarren C, Jacobs D, Sidney S, Gross MD, Eisner MD. Cigarette Smoking, Alcohol Consumption, and Risk of ARDS: a 15-year Cohort Study in a Managed Care Setting. CHEST 117(1):163-168, 2000.

C. Research Support

Completed:

R01-CA39742-16 (Folsom, Aaron) 03/01/2000-02/28/2005
10%

NIH \$599,863
Epidemiology of Cancer in a Cohort of Older Women: Iowa Women's Health Study.

Myron Gross, Co-investigator: This study will evaluate the risk factors of several cancers in women. A major focus is the risk factors for breast cancer. No overlap.

2 R01-HL53560-05 (Jacobs/Gross) 04/01/2000-03/31/2004
30%

NIH/NHLBI \$490,394
Epidemiology: Oxidative Stress and Early Atherosclerosis.

This study will evaluate a series of oxidative pathways in the CARDIA population. The oxidative damage will be evaluated associations with a series of cardiovascular disease endpoints and risk factors. A major endpoint will be subclinical disease as measured by electron beam computed tomography. No overlap.

N/A (Gross, Myron) 12/01/2000-5/30/2004 5%
AARP Andrus Foundation \$53,978
Nutrients and Successful Aging

Identify nutritional factors that may play a role in the maintenance of cognitive and physical function necessary for activities of daily living, specifically related to successful aging. No overlap.

(Gross, Myron) 07/01/2001-06/30/2005 2%
Health Excellence Fund \$18,702
Academia Coalition of Teens Against Tobacco

Educational interventions are evaluated for their effect on smoking behavior. The interventions are applied in teenagers and monitored throughout their high school years. No overlap.

BARBARA ANN
KARMANOS
CANCER INSTITUTE

Wayne State University | Detroit Medical Center

December 11, 2006

Flora A. M. Ukoli, MBBS, MPH, MPH
Department of Surgery
McHarry Medical College
1005 Dr. D. B. Todd, Jr. Bldg.
Nashville, TN 37211

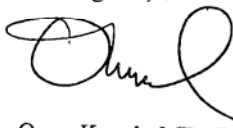
**RE: Lycopene supplementation in the complementary management of biochemical failure:
A phase II randomized trial for prostate cancer survivors**

Dear Dr. Ukoli:

I would be happy to participate as a co-investigator in your project "Lycopene supplementation in the complementary management of biochemical failure: A phase II randomized trial for prostate cancer survivors". The study is designed to assess the efficacy of two different lycopene supplements in preventing prostate cancer progression in men who have previously been treated for localized disease. It will compare a pure lycopene supplement with a tomato-extract supplement. I will assist you in conducting the study and help you in planning strategies for participant accrual and adherence. I have extensive experience in nutritional interventions with lycopene, tomato-extract and other micronutrients. I will be responsible for overseeing issues related to adverse effects, nutrient data analysis, biomarker analysis and interpretation. I will also contribute to the preparation of reports and manuscripts.

I look forward to working with you in this exciting project.

Best regards,



Omer Kucuk, MD, FACN
Professor of Medicine and Oncology

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format on preceding page for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Omer Kucuk	POSITION TITLE Professor		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
Hacettepe University Medical School, Turkey	MD	1969-1975	Medicine
St. Francis Hospital, Evanston, Illinois	Residency	1975-1978	Medicine
St. Francis Hospital, Evanston, Illinois	Fellowship	1978-1979	Hematology- Oncology
Northwestern University Medical School, Chicago, Illinois	Fellowship	1979-1981	Hematology- Oncology

Positions

1981 - 1984	Instructor, Department of Medicine, Section of Medical Oncology, Northwestern University Medical School, Chicago, IL.
1984 - 1988	Assistant Professor, Department of Medicine, Section of Oncology/Hematology, University of Health Sciences/The Chicago Medical School, North Chicago, IL.
1988 - 1991	Associate Professor, Department of Medicine, Section of Hematology/Oncology, University of Health Sciences/The Chicago Medical School, North Chicago, IL.
1991 - 1995	Professor, Department of Medicine, Section of Medical Oncology, University of Hawaii, John A. Burns School of Medicine, Honolulu, HI.
1995 - 2003	Professor of Oncology, Karmanos Cancer Institute (KCI), Wayne State University (WSU), Detroit
1995 - present	Professor of Medicine, Department of Medicine, Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI.
1995 - present	Member, Population Sciences and Prevention Program, KCI, WSU
1996 - present	Member, Cancer Biology Program, WSU
1998 - present	Professor (adjunct), Department of Nutrition and Food Science, WSU
2000 – present	Professor, Department of Otolaryngology – Head and Neck Surgery, WSU

Honors

2000	Research Excellence Award, Wayne State University
2000	Fellow, American College of Nutrition
2002	Editorial Board, Cancer Epidemiology Biomarkers and Prevention
2002-2004	Veterans Administration Merit Review Oncology Study Section Member

SELECTED PEER-REVIEWED PUBLICATIONS (FROM OVER 130)

1. Kucuk, O., Pandya, K., Skeel, R., Hochster, H., Abeloff, M. Phase II trial of cisplatin and 5-fluorouracil in previously treated advanced breast cancer: An ECOG pilot study. Breast Cancer Res Treat 57:201-206, 1999.
2. Jaszwski R, Khan A, Sarkar FH, Kucuk O, Tobi M, Zagnoon A, Dhar R, Kinzie J, Majumdar APN. Folic acid inhibition of EGFR mediated proliferation in human colon cancer cell lines. Am J Physiol 277: C1142-C1148, 1999.
3. Hussain M, Gadgeel S, Kucuk O, Du W, Salwen W, Ensley J. Paclitaxel, Cisplatin and 5-Fluorouracil in Patients with Advanced Squamous Cell Carcinoma of the Head and Neck. Cancer 86:2364-2369, 1999.
4. Davis, J.N., Kucuk, O., Sarkar F.H. Genistein inhibits NF-kappaB activation in prostate cancer cells. Nutr Cancer 35:167-174, 1999.

5. Kucuk, O., Young, M., Habermann, T., Wolf, B., Jimeno, J., Cassileth, P. Phase II trial of Didemnin B in previously treated non-Hodgkin's lymphoma: An Eastern Cooperative Oncology Group Study. *Am J Clin Oncol* 23, 2000.
6. Davis JN, Muqim N, Bhuiyan M, Kucuk O, Pienta KJ, Sarkar FH. Inhibition of prostate specific antigen expression by genistein in prostate cancer cells. *Int J Oncol* 16:1091-1097, 2000.
7. Kucuk O, Sarkar F, Sakr W, Djuric Z, Khachik F, Pollak M, Bertram J, Grignon D, Banerjee M, Crissman J, Pontes E, Wood DP Jr. Lycopene supplementation in men with localized prostate cancer: modulation of biomarkers and clinical endpoints. *Cancer Epidemiol Biomarkers Prev* 10:861-868, 2001.
8. Hillman GG, Forman JD, Kucuk O, Yudelev M, Maughan RL, Rubio J, Layer A, Tekyi-Mensah S, Abrams J, Sarkar FH. Genistein potentiates radiation effect on prostate carcinoma cells. *Clin Cancer Res* 7:382-390, 2001.
9. Davis JN, Kucuk O, Sarkar FH. Effect of soy isoflavone supplementation on NF-kB activation in healthy human subjects. *Free Rad Biol Med* 30:1293-1302, 2001.
10. Djuric Z, Chen G, Sarkar F, Doerge D, Heilbrun L, Kucuk O. Effect of soy supplementation on oxidative stress in men and women. *Cancer Lett* 172:1-6, 2001.
11. Fleshner NE, Kucuk O. Antioxidant dietary supplements: Rationale and current status as chemopreventive agents for prostate cancer. *Urology* 57(4 Suppl 1):90-94, 2001.
12. Kucuk O. New opportunities in chemoprevention research. *Cancer Investigation* 20 (2): 237-245, 2002.
13. Nagothu KK, Jaszewski R, Moragoda L, Rishi AK, Finkenauer R, Tobi M, Naumoff JA, Dhar R, Ehrinpreis M, Kucuk O, Majumdar AP. Folic acid mediated attenuation of loss of heterozygosity of DCC tumor suppressor gene in the colonic mucosa of patients with colorectal adenomas. *Cancer Detection and Prevention* 27:297-304, 2003.
14. Kucuk O, Sarkar F, Sakr W, Khachik F, Djuric Z, Banerjee M, Pollak M, Bertram J, Wood DP Jr. Lycopene in the treatment of prostate cancer. *Pure Appl Chem* 74:1443-1450, 2002.
15. Beck FWJ, Prasad AS, Butler CE, Sakr WA, Kucuk O, Sarkar FH. Differential expression of hZnT-4 in human prostate tissues. *Prostate* 58:374-381, 2004.
16. Hussain M, Sarkar FH, Djuric Z, Pollak MN, Banerjee M, Doerge D, Fontana J, Chinni S, Davis J, Forman J, Wood DP, and Kucuk O. Soy isoflavones modulate serum PSA level in patients with prostate cancer. *Nutrition & Cancer* 47:111-117, 2003.
17. Hussain M, Banerjee M, Sarkar FH, Djuric Z, Pollak MN, Doerge D, Fontana J, Chinni S, Davis J, Forman J, Wood DP, and Kucuk O. Soy isoflavones in the treatment of prostate cancer. *Nutrition & Cancer* 47:111, 2003.
18. Li Y, Che M, Bhagat S, Ellis KL, Kucuk O, Doerge DR, Abrams J, Cher ML, Sarkar FH. Regulation of Gene Expression and Inhibition of Experimental Prostate Cancer Bone Metastasis by Dietary Genistein. *Neoplasia*. 6:354-363, 2004.
19. Li Y, Ellis KL, Ali S, El-Rayes BF, Nedeljkovic-Kurepa A, Kucuk O, Philip PA, Sarkar FH. Apoptosis-inducing effect of chemotherapeutic agents is potentiated by soy isoflavone genistein, a natural inhibitor of NF-kB in BxPC-3 pancreatic cancer cell line. *Pancreas* 28:E90-E95, 2004.
20. Hillman GG, Yu Wang, Kucuk O, Che M, Doerge DR, Yudelev M, Joiner MC, Marples B, Forman JD, Sarkar FH. Genistein potentiates inhibition of tumor growth by radiation in a prostate cancer orthotopic model. *Molecular Cancer Ther* 3:1271-1279, 2004.
21. Xu H, Yu Y, Marciniak D, Rishi AK, Kucuk O, Sarkar FH and Majumdar APN. EGFR-Related Protein (ERRP) Inhibits Multiple EGFR members in Colon and Breast Cancer Cells. *Molecular Cancer Ther* 4:435-442, 2005.
22. Li Y, Ahmed F, Ali S, Philip PA, Kucuk O, Sarkar FH. Inactivation of nuclear factor-kappaB by soy isoflavone genistein contributes to increased apoptosis induced by chemotherapeutic agents in human cancer cells. *Cancer Res* 65(15):6934-42, 2005.
23. Mohammad RM, Banerjee S, Li Y, Aboukameel A, Kucuk O, Sarkar FH. Anti-Tumor Activity of Cisplatin is Potentiated by Soy Isoflavone Genistein in BxPC-3 Pancreatic Tumor Xenografts. *Cancer* 2006.
24. Li Y, Kucuk O, Hussain M, Abrams J, Cher ML, Sarkar FH. Antitumor and antimetastatic activities of docetaxel are enhanced by genistein through regulation of osteoprotegerin/receptor activator of nuclear factor-kappaB (RANK)/receptor activator of nuclear factor kappaB ligand (RANKL)/matrix metalloproteinase-9 (MMP-9) signalling in prostate cancer. *Cancer Res* 66:4816-4825, 2006.

CURRENT RESEARCH SUPPORT

Completed:

NO1-CN-85083 (Kucuk, Omer, PI)

07/01/03 - 12/31/06

10%

NCI

\$ (annual direct)

Phase II Clinical Studies of Chemopreventive Agents

Title: Modulation of Growth and Differentiation in Prostate Cancer with Soy Isoflavones

This project is to investigate *in vivo* effects of soy isoflavones on human prostate tissues. Men with prostate cancer are randomly assigned to receive soy isoflavones or placebo. Biomarkers are analyzed on prostate and blood specimens.

NO1-CN-05022-57 (Kucuk, Omer, PI)

10/01/02 - 12/31/06

20%

NCI

\$(total direct)

Phase II Clinical Studies of Chemopreventive Agents

Title: Randomized Clinical Trial of Zileuton in Persons with Bronchial Dysplasia

The major goal of this project is to investigate *in vivo* effects of zileuton, a *5-lipoxygenase inhibitor*, on human bronchial dysplasia. Smokers with biopsy-proven dysplasia are randomly assigned to receive zileuton or placebo for 6 months and crossed over to the opposite arm for 6 months and bronchoscopic biopsies and blood samples are obtained for analysis.

Appendix 12: Protocol Final Draft: (A 2-Arm study with revised title.)**Clinical Protocol:**

1. Protocol Title: Lycopene supplementation in the complementary management of Biochemical failure: A phase II randomized trial for prostate cancer survivors
2. Phase: Phase II.
3. Principal Investigator:
Flora A. M. Ukoli, MBBS, DPH, MPH.
(Associate Professor: Community Medicine/Epidemiology)
Department of Surgery, Meharry Medical College
1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37208
Tel. 615-327-5653 Fax: 615-327-5579 Email: fukoli@mmc.edu

4. Roles and Responsibilities of Research Personnel

Name	Highest Degree (License)	Job Title	Employing Institution	Responsibility (% Effort)
Flora Ukoli	MBBS, MPH.	Associate Professor	MMC	PI, Epidemiologist (25%)
Ronald Davis	M.D. (0000016734)	Professor	MMC	Inv, Urologist (10%)
Lavenia Crutcher	RN. (0000040674)	Research Coordinator	MMC	Coordinator (20%)
Anthony Archibong	Ph.D.	Associate Professor	MMC	Inv, Biochemistry (5%)
Emeka Ikpeazu	M.D., Ph.D. (0000026474)	Assistant Professor	MMC	Inv, Oncologist (3%)
Derrick Beech	M.D. (0000031467)	Professor	MMC	Inv, Surgery (3%)
Jay Fowke	Ph.D.	Assistant Professor	VUMC	Co-PI, Epi/Nutrition (7.5%)
Saundra Motley	RN., MBA. (0000032062)	Research Coordinator	VUMC	Coordinator (20%)
Bonnie LaFleur	Ph.D.	Assistant Professor	VUMC	Inv, Statistics (5%)
Jason Morrow	M.D., Ph.D. (0000017815)	Professor	VUMC	Inv, Pharmacology (2%)
Michael Cookson	M.D. (0000030345)	Assistant Professor	VUMC	Inv, Urologist (5%)
Myron Gross	Ph.D.	Associate Professor	UM	Inv, Biochemistry (3%)
Omer Kucuk	M.D. (4301037887)	Professor	WSU	Inv, Oncology (3%)

Employing institutions of study investigators:

Meharry Medical College, Nashville, TN.
Vanderbilt University Medical College, Nashville, TN.
University of Minnesota, Minneapolis, MN.
Wayne State University, Detroit, MI.

MMC
VU
UM
WSU

Brief description of the duties of study personnel

- Ukoli, F. PI: Responsible for all research related administrative activities, protocol implementation, identify additional urologists and patients for the study, supervise research staff, responsible for data analysis and interpretation, prepare reports and write manuscripts.
- Davis, R. Study urologist: Inform patients about the study, provide consultation and patient follow-up, source for cooperation of other urologists, data interpretation, and preparation of manuscripts
- Crutcher, L. Nurse coordinator at MMC: Assist PI to guide the protocol through the MMC IRB, educate, accrue, and consent participants, and implement protocol at Meharry. Follow-up participants and monitor adverse events. Coordinate activities with study coordinator at Vanderbilt.
- R/A at MMC: Assist PI to implement study, recruit and interview participants, process and ship samples to various laboratories, data collection and entry.
- Archibong, A. Laboratory support: Provide expertise in the handling of samples, conduct laboratory analysis, involved in data interpretation & manuscript preparation.
- Ikpeazu, E. Inform patients about the study, provide oncology consultation, source for cooperation of other oncologists, and manuscript preparation.
- Beech, D. Community networking, establishing trust with community leaders, ensure institutional support, involved in data interpretation and manuscript preparation.
- Fowke, J. Co-PI. Responsible for research related administrative activities, protocol implementation, and supervision of research staff at Vanderbilt, involved in data analysis & interpretation, and preparation of reports and manuscript.
- LaFleur, B. Statistical support, sample size calculation, data management & analysis, data interpretation, and involved in manuscript preparation.
- Morrow, J. Laboratory support for the measurement of isoprostane, expertise in data interpretation and manuscript preparation.
- Cookson, M. Study urologist at VU: Inform patients about the study, consultation and patient follow-up, source for the cooperation of other urologists at Vanderbilt, involved in data analysis & interpretation, and preparation of manuscripts.
- Motley, S. Nurse coordinator at VU: Direct and coordinate study, guide the protocol through the VU IRB and the HSRRB, recruit and consent participants, implement protocol, follow-up participants, coordinate activity with the study pharmacist and research staff at MMC, collect data, monitor adverse events, assist the PI, and train research staff at MMC.
- Gross, M. Laboratory support to measure lycopene, expertise in data interpretation, and manuscript preparation.
- Kucuk, O. Expertise in study design, protocol development, dietary supplement intervention strategies, and protocol implementation. Assist the PI to acquire supplements. Involved in data interpretation and manuscript development.

Medical Monitor: Alphonse Pasipanodya, M.D., Associate Professor, Department of Surgery,
(TN License MD0000010137):

5. Location of Study: (List all centers, clinics, or laboratories where the study is to be conducted. Be sure that the name, degree(s), title, employing institution, and complete address of the investigator(s) for each site is included above.)

Study participants will be recruited from two institutions:

- i) Meharry Medical College, Nashville, Tennessee.
Flora A. M. Ukoli, MBBS, DPH, MPH.,
(Associate Professor: Community Medicine/Epidemiology)

Department of Surgery, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37208.

Tel. 615-327-5653 Fax: 615-327-5579 Email: fukoli@mmc.edu

- ii) Vanderbilt University Medical Center, Nashville, TN.

Jay H. Fowke, PhD. (Assistant Professor)

Vanderbilt Epidemiology Center, Division of Internal Medicine and Public Health
1215 21st Street South

Vanderbilt University Medical Center, 6110 Medical Center East

Nashville, TN 37232-8300

Ph: 615-936-2903 Fax: 615-936-1269 Email: jay.fowke@Vanderbilt.Edu

Laboratory analysis will be conducted at Meharry, Vanderbilt, and Minnesota.

- iii) Anthony Archibong, Ph.D. (Associate Professor)

Department of OB/GYN, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd.
Nashville, TN 37208.

Tel. 615-327-5714 Fax: 615-327- Email: aachibong@mmc.edu

- iv) Jason D. Morrow, M.D. (Professor)

Division of Clinical Pharmacology, 536 Robinson Research Building 23rd Ave S @
Pierce

Nashville, TN. 37232-6602

Ph: 615.322.4785 Fax: 615.343.9659 Email: jason.morrow@Vanderbilt.Edu

- v) Myron D. Gross, Ph.D. (Associate Professor)

University of Minnesota, Division of Epidemiology

1300 South Second Street, Suite 300, Minneapolis, MN 55454

Ph: 612-624-5417 Fax: 612-624-2959 Email: gross@epi.umn.edu

Research collaboration & consultation at Wayne State University.

- vi) Omer Kucuk, MD., FACN (Professor of Medicine & Oncology)

Division of Hematology and Oncology, Karmanos Cancer Institute

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6. Time required to complete study.

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7. Background.

Rationale for conducting this study:

African-American men have the highest rates of prostate cancer incidence and mortality in the world. Whites and Asians who have migrated to America from low incidence regions such as Japan have acquired prostate cancer rates similar to that of the host country, suggesting that environmental and dietary factors might be more important than genetics in the progression of this disease. High tumor grade and stage at diagnosis are important risk factors of prostate cancer mortality while black race is linked to socio-economic status (SES) and disparity to preventive and curative health care access. Prostate cancer mortality can therefore be reduced by providing access to early detection and by manipulation of environmental risk factors of cancer progression. So far

surgery and radiation are equally effective for long-term survival. However the best treatment outcome is reported for a combination of both methods, surgery plus postoperative radiotherapy, as opposed to surgery alone or radiation alone, and this is most evident in patients with high-grade tumors. However some patients do present with progressive disease, the early indication of which is biochemical (PSA) recurrence. It is therefore possible to expect additional increase in survival time when complementary inhibition of carcinogenesis by chemopreventive or dietary intervention methods is included in the treatment plan. Although tumor grade is a good predictor of high-risk prostate cancer, biochemical recurrence is a more objective measure of high-risk, and so this trial plans to investigate the effectiveness of complementary intervention to inhibit carcinogenesis among patients who have developed biochemical recurrence.

It has been reported that saturated fat from animal sources is associated with increased prostate cancer risk, while antioxidants such as selenium, vitamin E and carotenoids like lycopene that tend to be associated with reduced prostate cancer risk, are said to be protective. Lycopene is an antioxidant derived mainly from tomato-based foods, and the plasma levels have been reported to be lower in American blacks compared to whites. Although the exact mechanism of action within the prostate is not yet clear, there is sufficient evidence from laboratory and epidemiologic research to suggest that lycopene may inhibit prostate cancer progression. Prostate cancer survivors who have been treated successfully by surgery or radiation can present with biochemical (PSA) failure after several years of being cancer free. This condition affects both black and white men even though they have diverse ethnic dietary styles. This study is a feasibility study to investigate the effects of increased plasma lycopene by nutrient supplementation on PSA failure among African-American men. A similar study that recruited mainly Caucasian men did not find substantial effects on PSA, this may not be true for African-Americans who already have lower plasma levels of lycopene.

While some investigators believe in the potency of individual single nutrients for the health of various body organs and functions, others believe that these nutrients all work together in concert for overall optimum health. Men in general, and those who have been diagnosed with prostate cancer in particular, are currently exposed to, and are responding to advertisements about dietary and other supplements proposed to 'be good for prostate health' and 'to protect the prostate gland'. This study will provide pilot data to inform investigators and patients about the usefulness of lycopene, either as a single nutrient supplement, or as derived from a whole-food tomato-extract supplement, in prostate cancer control. Pilot data from this study will be used to seek funding to increase the study sample size, increase the intervention and follow-up period, include men from other ethnic minorities, and to conduct similar studies in men with metastatic prostate cancer. Currently the management of prostate cancer does not include a dietary component. If results from larger studies indicate the usefulness of dietary antioxidants then it can be proposed as part of routine management for both African-American and Caucasian men undergoing treatment for prostate cancer, especially those who have low plasma lycopene levels to start with.

Preliminary diet frequency consumption data among black men in the Washington DC area suggests low intake of tomato-based foods ranging from 1-4 servings of tomato/spaghetti sauce per month among African-Americans (Ukoli, F.A. Unpublished). The PI has assembled a team of investigators across the Meharry-Vanderbilt Alliance with interests in cancer prevention and experience in clinical trials to develop and implement this supplement intervention among African-American men in Nashville. Since cooked tomato such as tomato-sauce, is the richest source of bioavailable lycopene, one would have suggested increasing dietary consumption of cooked tomato to increase plasma lycopene. Besides consuming entrees prepared with tomato-sauce might be a simple, safe, low-cost strategy for reducing the risk of prostate cancer progression. However changing dietary habits can be a challenge, and might and probably not be convenient especially

among adults who have established eating styles. Tomato-extract supplements appear to be a convenient substitute for tomato-based food for people wishing to increase plasma lycopene levels without changing their dietary style. This study proposes to compare the effect of tomato-extract supplement and single nutrient lycopene in the inhibition of prostate cancer progression.

This study will specifically address lycopene supplementation without manipulating dietary life-style, and it will only target men with biochemical (PSA) failure following initial treatment by radical prostatectomy or radiation. However the findings may be relevant for those who had other forms of treatment, and may also be a useful strategy for preventing biochemical failure.

Literature Review:

Prostate Cancer Epidemiology:

Cancer continues to be the second leading cause of death in America, second only to cardiovascular disease, and prostate cancer remains the second leading cause of cancer deaths among men in the last two decades. Prostate cancer deaths are especially prominent among men 60 and older, and as life expectancy continues to improve prostate cancer mortality will become even more important. Cancer incidence and mortality varies considerable among racial and ethnic groups, African-American men recording 23% higher incidence and 40% higher death rates than their White counterparts. African-American men have the highest incidence of prostate cancer in the world, and mortality among African-Americans is approximately 2-fold higher than in White men (1,2). While the effect of screening by prostate specific antigen test (PSA) and digital rectal examination (DRE) that started in the early 80s led to increased diagnosis of early stage cancer across all ethnic groups especially among White men, the ethnic disparity in mortality rates have remained, and several reasons have been put forward to explain this situation. Failure to receive screening and detect prostate cancer in its early more treatable stage can account for increased prostate cancer mortality among African-Americans, but the disparity remained across all stages of prostate cancer. Prostate cancer mortality rates for blacks diagnosed with localized, regional, distant, and unstaged disease were 1.9, 1.5, 2.4, and 2.0 times those of for whites (3,4). Ethnic disparity in prostate cancer incidence is reported to be as a consequence of disparity in genetic predisposition, exposure disparity to various potential risk and protective factors that initiate or promote prostate carcinogenesis. Marked racial and geographic differences are probably due to genetic, environmental, and social influences that may affect the progression or prostate cancer. Dietary influences, hormonal milieu, and environmental carcinogens are probably more important than familial inheritance in this instance (5,6).

The prevalence of prostate cancer continues to rise in the light of improved life expectancy, and more awareness and screening by PSA and DRE. Population-based prostate cancer rates increased by 70% between 1988 and 1991, a majority of men being diagnosed with local disease that is treatable, leading to about 185,000 prostatectomies in a year. Survival rates following radical prostatectomy have been extremely encouraging, 84%, 72% and 61% at the 5-, 10- and 15-years time-points are. Increase in prostate cancer survival over the same period was observed across all ethnic groups and is believed to be as a result of lead-time bias, over-diagnosis, and the possible benefits of screening. Of the nearly ten million cancer survivors in the United States, 17.0% have prostate cancer and 10.9% of these are African-Americans (7–11,12). Fewer men are diagnosed with advanced disease, and survival outcomes vary with treatment options, which in turn depend on patient selection criteria. Patients have been compared across age, treatment, and pre-treatment risk groups, both for prostate specific and non-prostate specific mortality. Mortality is affected by age and pre-treatment risk, but reports about the outcome by either prostatectomy or brachytherapy remain controversial. Some studies support one form of treatment over the other, but in general intermediate- and high-risk patients have more durable biochemical outcomes when managed by

brachytherapy, with or without external-beam radiation therapy, while outcome for low-risk patients are comparable or better for radical prostatectomy. Both methods score similarly in terms of general health-related quality of life after treatment (13-16). Patients who undergo radical prostatectomy tend to have more sexual and urinary dysfunction than those who had external beam radiation therapy, the later reporting worse bowel function and more irritative urinary voiding symptoms. The same remains true for those treated by brachytherapy as they report less urinary leakage, but experience considerably more irritating voiding symptoms. In general men treated for prostate cancer have more of these quality of life (QOL) problems in comparison with age-matched controls, but pre-treatment baseline function levels are very relevant when evaluating post-treatment QOL (17,18). These distressing QOL issues are extremely important and must be addressed to meet the needs of this growing population of prostate cancer survivors, who in addition may have to face the threat of cancer progression in the form of biochemical recurrence or PSA failure.

Biochemical Recurrence (PSA Failure):

PSA failure is clinically defined as three consecutive rising PSA after undetectable levels following radical prostatectomy or above the lowest value attained (nadir) following radiation therapy, or at least one PSA test above 0.4ng/ml (19,20). The rate of developing biochemical failure is reported at 15% at the 15-year post-radical prostatectomy survival time-point. Biochemical failure is a significant index of prostate cancer recurrence, and it is predicted by age, pretreatment PSA > 20 ng/ml, and Gleason score 7-10. In survival analysis, time to biochemical progression ($P<.001$), Gleason score ($P<.001$), and PSA doubling time ($P<.001$) were all predictive of the probability and time to the development of metastatic disease. Without any intervention more than a third of the patients will develop metastatic disease within 5 years, and up to 65% will develop metastasis by 10 years. The median interval from PSA failure to cancer death ranges from 5 – 12 years, median actuarial time to metastases being 8 years (21). Biochemical failure occurs earlier in patients treated by radiation, and is reported to up to 10% at the 3-year time-point, while at 5 years post-treatment, failure rate can be up to 24.4% for patients treated with brachytherapy, and 21.2% for those treated with external beam radiation. For high-grade prostate cancer of Gleason 8-10, the respective rates for biochemical failure 5 years after treatment can be as high as 48% and 62% (22,23). The rate of biochemical failure among patients with high-grade prostate cancer is uniformly poor across treatment modalities, and studies have reported 5-year biochemical failure rates of 35%, 70% and 80% respectively for patients treated with surgery plus postoperative radiotherapy, radiotherapy alone, and surgery alone (24). When computer-generated matching was performed to create two identical cohorts of White Americans and African-Americans, race was not found not be a significant independent predictor of biochemical failure (25).

Prognosis for biochemical failure depends on the age of the patient, the tumor grade and stage among other variables. Also treatment choice depends on these same variables in addition to the presence of co-morbidities. It is therefore necessary to take all these factors into account in the study of the natural history of biochemical failure. For example, radical prostatectomy is the most usual choice of treatment for young healthier men, and should result in the best long-term rates for biochemical free survival. On the underhand this will give rise to a higher rate of PSA failure for younger patients with higher tumor grade and cancer stage (26). The treatment option for PSA failure includes androgen deprivation, cryotherapy, and salvage radiation. Overall survival after PSA-detected recurrence following conformal radiation therapy was 58% at five years while cause specific survival was 73%, even though these patients have worse than average pre-radiation prognostic factors. Therefore it is necessary to be cautious in the consideration of rather toxic salvage treatment especially for those with longer PSA doubling time, and smaller relative PSA rise (27). Salvage radiotherapy for radical prostatectomy patients presenting with biochemical failure

resulted in 80% 8-year survival, with only 35% remaining free of PSA relapse (28), and in a second series only 33% were free of PSA relapse at 6 years with a 14% actuarial probability of distant metastasis (29). Although salvage prostatectomy provided excellent control for patients who presented with radio-recurrent prostate cancer that was organ-confined or that involved the immediate periprostatic tissue, best results are expected for those treated before PSA rises above 10ngs./ml (30).

Chemoprevention is the administration of pharmacological agents to prevent, delay or reverse carcinogenesis. Anti-oestrogens have been used to reverse high grade intraepithelial neoplasia in breast carcinogenesis, and anti-androgens have also been used in the same way for prostate carcinogenesis. Several epidemiological studies do suggest that the consumption of dietary anti-oxidants like vitamins D and E, soy, lycopene and selenium may be protective. The consensus has provided the need to investigate these agents in randomised, placebo-controlled trials, especially among high-risk individuals (31). Androgen ablation, neoadjuvant, adjuvant and intermittent therapy, using drugs or surgery to produce castrate levels of testosterone inhibits prostate cancer cell growth. Previously only patients with advanced, metastatic or recurrent prostate cancer received androgen ablation until death, with a median survival of 3 years. Now that prostate cancer recurrence is diagnosed on the basis of PSA failure the median life expectancy for such patients is 10-15 years. Androgen ablation therapy improves patient survival, but it is not curative, is associated with substantial adverse impact on the quality of life for patients, especially with prolonged use as will be the case for those with PSA recurrence, and some patients will develop hormone-refractory disease. Controversy still exists with respect to the timing of this therapy, the use of intermittent androgen ablation, and the role of total androgen blockade. The challenge is to develop better means to avert hormone-refractory prostate carcinoma and better treatments for when it occurs (32). Longer periods of PSA relapse free survival can be achieved with combined modality treatment using hormonal therapy with brachytherapy and external beam radiation. In this study 5-year PSA recurrence was avoided in 76% of patients with Gleason score 8-10, 97% of those with Gleason score < 6, and 74% for patients with seminal vesicle involvement (33).

PSA Recurrence

Dietary and Prostate Carcinogenesis:

Comparative autopsy studies across nations have shown that the incidence of latent prostate cancer is the same in low-incidence countries like Japan and Singapore and in high-incidence regions like among populations of African-Americans. The worldwide incidence of clinical prostate cancer differs greatly across these nations. In countries with low incidence and mortality rate, the foci of the latent prostate cancer are small and show only slight tendency to proliferate, but in high-incidence high-mortality countries the foci are frequently larger and more aggressive. The international disparity in the pattern of latent and clinical prostate cancer incidence therefore indicate differences in exposure to cancer promoting and malignant transformation factors such as environmental and dietary factors, rather than differences in cancer initiation factors (34). The association between dietary fat and cancer, especially of the colon, breast, prostate, and ovary has been suspected for several decades, and has been demonstrated by ecologic and migrant studies. Several epidemiological studies have indicated dietary fat as a likely risk factor for prostate cancer. There is no solid evidence that this effect is mediated through the effect of hormones on the prostate. Comparing the levels of various hormones such as estradiol, estrone, prolactin and testosterone in prostatic fluid and serum are not conclusive because of the confounding role of plasma protein binding (35, 36). At the individual level statistically significant association has been demonstrated between total dietary fat intake and prostate cancer risk across all ethnic groups. Saturated fat was found to be responsible for this association while monounsaturated fat was only weakly associated, and protein, carbohydrate, polyunsaturated fat, and total dietary energy intake were not associated

with prostate cancer risk. The risk of prostate cancer from saturated fat increased independent of length of residence among foreign-born Asian-Americans. While other factors are concluded to be largely responsible for ethnic disparity in risk, saturated fat intake is estimated to account for 10% black : white differences and about 15% white : Asian-American differences in prostate cancer incidence (37).

In a case-control study of 932 newly diagnosed prostate cancer cases, 449 black and 483 white, men) that collected dietary information with special focus on animal products and animal fat, increased consumption (grams/day) of foods high in animal fat was associated with prostate cancer risk among American blacks [by quartile of intake, odds ratio (OR) = 1.0 (referent), 1.5, 2.1, and 2.0; P_{trend} = 0.007], but not among American whites [by quartile of intake, OR = 1.0 (referent), 1.6, 1.5, and 1.1; P_{trend} = 0.90]. This association was independent of intake of other calories. A higher level of risk was observed between advanced prostate cancer and consumption of foods high in animal fat content, and this finding was significant both for blacks and whites (38). A large prospective cohort study of 47,866 American men 40-75 investigated the effects of consuming specific fatty-acids, alpha-linolenic (ALA; 18:3n-3), eicosapentaenoic (EPA; 20:5n-3), docosahexaenoic (DHA; 22:6n-3), linoleic (LA; 18:2n-6), and arachidonic (AA; 20:4n-6) on prostate cancer risk. They followed the cohort for 14 years, and during that period 2,965 prostate cancer cases developed, with 448 classified as advanced prostate cancer. Using multivariate relative risk analysis this study concluded that LA and AA intake was unrelated to the risk of prostate cancer, while EPA and DHA intakes were protective against prostate cancer risk. However they observed that increased dietary intake of ALA may increase the risk of advanced prostate cancer (39). These protective fatty-acids are found in fish and are referred to as marine fatty-acids. Eating fish more than three times per week was associated with a reduced risk of prostate cancer, and the strongest association was for metastatic cancer. Marine fatty acids may account for part of the effect, but other factors in fish may also play a role (40). The importance of whole dietary style was explained in a case-control study that found no association with total monounsaturated fatty-acids (MUFA), but reported independent protective ability for consumption of higher amounts vegetable oils rich in MUFA, which were also rich in vegetables, lycopene, vitamin E, selenium, and n-3 fish oils. This finding may be explained by the protective effect of an associated dietary pattern high in antioxidants and fish oils, an independent protective effect of MUFA-rich vegetable oils unrelated to the MUFA component, or a combination of these factors (41). Body fat and physical inactivity per se have been incriminated in the etiology of prostate cancer risk. Since dietary intake and physical activity are both closely linked with body fat distribution all three factors need to be studied simultaneously to understand the mechanism by which they affect prostate cancer risk (42,43).

Diet May Inhibit Prostate Carcinogenesis:

Antioxidants, including carotenoids, retinoids, polyphenols, selenium, vitamin E, C, D, calcium and lycopene have all been reported to protect against prostate cancer by inhibiting cancer cell proliferation, differentiation and signaling related to cancer initiation, progression and regression (44,45). In this small follow-up study low plasma levels of antioxidant vitamins A, C, and E and carotene were associated with overall cancer mortality, and this effect was stronger in men above age 60 years at blood sampling (46). These findings are not always confirmed as in a nested case-control study of age and race matched controls of 103 men who developed prostate cancer during a 13-years follow-up of 25,802 persons in Washington County, MD. Inverse association was observed for serum retinol and risk of prostate cancer, but not for beta-carotene, lycopene, and tocopherol (vitamin E) (47). The variation in findings may be a result of how the data was analyzed, as well as the characteristics of the study population. This nested case-control study found a statistically significant protective association between higher plasma lycopene and prostate

cancer only for older men and those with sporadic prostate cancer, but not for those with a family history of prostate cancer. They also reported diets rich in beta-carotene may also play a protective role in prostate carcinogenesis among younger men (48).

Since the intake of specific foods such as margarine have been positively associated with prostate cancer risk, while others like allium vegetables, tomato-based foods, and total vegetables appear to be protective, diets rich in olive oil (a source of oleic acid), tomatoes and allium vegetables have been proposed to reduce the risk of prostate cancer (49). These suggestions are underscored by the long standing history of low prostate cancer rates reported among Asian migrants in America (50). Also very strong support for the protective effect of these food items have been based on results demonstrated in laboratory studies of the TRAMP mice model which has been developed to test chemopreventive agents on human prostatic cancer cell lines DU145 and PC3. In this study anti-oxidants found in spinach leaves and a green tea were tested as to their ability to slow spontaneous tumorigenic progression both in the TRAMP mice and the wild-type male mice. Sacrifices occurred on weeks 5, 9, and 13. Prostatic histopathology and oxidative-stress blood markers were evaluated. They agents were found to have anti-oxidative and antiproliferative properties and were able to slow the spontaneous prostatic carcinogenic process (51).

Lycopene and Prostate Cancer:

Evidence from animal models or cultured cancer cells demonstrate that lycopene inhibit prostate carcinogenesis by trapping singlet oxygen, inhibiting cancer cell growth through a growth factor receptor signaling mechanism. Dietary intakes of tomato products have been shown to be associated with decreased risk of cancer in numerous studies. Serum and tissue lycopene levels have also been inversely related to the risk of prostate cancer. Lycopene functions as a very potent antioxidant, by trapping singlet oxygen, and has been shown to reduce mutagenesis. Lycopene can inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression at physiological concentrations. Studies using human and animal cells have identified a gene, connexin 43, whose expression is upregulated by lycopene and which allows direct intercellular gap junctional communication (GJC). GJC is deficient in many human tumors and its restoration or upregulation is associated with decreased proliferation (52).

The other mechanism by which lycopene protects against prostate cancer is the effect on cell growth or survival, cell cycle progression, and apoptosis as demonstrated in the LCNaP human prostate cancer cell line. In comparison with placebo, lycopene arrested the cell cycle and produced apoptosis (53,54). When lycopene and vitamin E were tested in the MatLyLu Dunning prostate cancer model, plasma levels comparable with those in humans were attained, and both compounds were accumulated in the tumor tissue, and caused tumor necrosis. While Vitamin E reduced androgen signaling without affecting androgen metabolism, lycopene interfered with local testosterone activation by down-regulating 5-alpha-reductase and consequently reduced steroid target genes expression. Lycopene also down-regulated prostatic IGF-I and IL-6 expression. It is suggested that lycopene and vitamin E inhibit prostate cancer growth by interfering with internal autocrine or paracrine loops of sex steroid hormone and growth factor activation/synthesis and signaling in the prostate (55, 56). These ability to reduce normal and cancerous cell proliferation, DNA damage, and the ability to improve oxidative stress can be organ specific (57). Although numerous studies have demonstrated these cancer inhibitory effects, some studies have not been able to confirm the chemopreventive ability of lycopene (58).

Lycopene has been shown to have synergistic action with various carotenoids, alpha-tocopherol and other antioxidants. The effects of 15 kinds of carotenoids on the viability of three lines of human prostate cancer cells, PC-3, DU 145 and LNCaP, were evaluated and found to

significantly reduce cell viability. Several of these carotenoids such as phytofluene, zeta-carotene and lycopene which are present in tomato significantly reduced cell viability. Neoxanthin and fucoxanthin were found to reduce cell viability through apoptosis. However, phytoene, canthaxanthin, beta-cryptoxanthin and zeaxanthin did not affect the growth of the prostate cancer cells (59). Using two different human prostate carcinoma cell lines (the androgen insensitive DU-145 and PC-3), lycopene alone was not a potent inhibitor of prostate carcinoma cell proliferation, but together with alpha-tocopherol, a strong inhibitory effect of prostate carcinoma cell proliferation was observed. This synergistic effect of lycopene with alpha-tocopherol was not shared by beta-tocopherol, ascorbic acid or probucol (57,60).

The development of chemopreventive agents against prostate cancer would benefit from conclusive evidence of their efficacy in animal models that emulate human disease. The 12T-10 Lady transgenic model spontaneously develops localized prostatic adenocarcinoma and neuroendocrine cancer followed by metastases, recapitulating the natural history of human prostate cancer in many respects (61). Using male Lady version of the transgenic adenocarcinoma of the mouse prostate mice, administration of antioxidants (vitamin E, selenium, and lycopene) in the diet dramatically resulted in a 4-fold reduction in the incidence of prostate cancer compared with the untreated animals, and increased disease free survival. The micronutrients were well tolerated with no evidence of antioxidant-related toxicity (62). Since lycopene also inhibits normal prostate epithelial cell growth in vitro it may also be useful in controlling benign prostate hyperplasia, a potential precursor of prostate cancer, forming the basis for several lycopene prostate cancer intervention studies in human populations (63).

The significance of the geometric isomeric form in which lycopene exists in the human body is not clear. In tomatoes, tomato paste, and tomato soup lycopene exists mainly as all-trans lycopene (about 85%) and only about 15% exists in the cis-form of lycopene. Lycopene concentrations in the serum of men range between 0.60 and 1.9 nmol/ml, with about one-third as all-trans lycopene and two-thirds in the cis-isomer form. In striking contrast with foods, all-trans lycopene accounts for only 12-21% and cis isomers for 79-88% of total lycopene in benign or malignant prostate tissues (64). Although few case-control studies reported no evidence of a protective effect of lycopene for prostate cancer (65,66), or only a weak association (67), several investigators have reported convincing findings from case-control, cohort, and nested case-control studies that greater lycopene intake from tomato-based foods reduce prostate cancer risk (46-49, 68-71). Several large cohort studies have been conducted in the United States (68-71), the Netherlands (72), the UK (73), Hawaii (74) and China, a prostate cancer low-incidence region (75), have shown convincing evidence that lycopene does inhibit prostate cancer. These views are published in several review articles to support the protective role of dietary lycopene for prostate cancer risk (76-80).

Lycopene and Prostate Cancer Risk in Black Men:

The serum levels of individual carotenoids in 209 cases and 228 controls that included comparable numbers of Black and White men aged 40-79 years were analyzed to further search for reasons prostate cancer incidence is over 50% higher in US Blacks than Whites. Lycopene was found to be inversely associated with prostate cancer risk, particularly for the aggressive form of the disease. While the level of other carotenoids were similar for Blacks and Whites, serum lycopene concentrations were significantly lower in Blacks than in Whites, raising the possibility that differences in lycopene exposure may contribute to the racial disparity in incidence. This difference was not statistically significant (81). In a population-based case-control study of men aged 65-79 years conducted by telephone interviews, Caucasian men working in production, transportation, and material moving had increased prostate cancer risk while African-American men in the military had

reduced prostate cancer risk. Higher level of lycopene consumption was associated with a reduced risk of prostate cancer among Caucasian men, but not among the African-American men. This study did not find marked differences in lifestyle factors associated with prostate cancer risk by race (82).

In a review of pertinent literature on the prospective ability of lycopene on prostate cancer it was concluded that the benefit may be most pronounced in the protection against more advanced or aggressive prostate cancer. Food processing does not seem to reduce the benefits but may, in fact, enhance the bioavailability of antioxidants. On the basis of the strong evidence consumption of tomato products at approximately one serving per day or five servings per week was recommended as part of an overall healthy dietary pattern that may reduce the risks of prostate cancer, other malignancies, or other chronic diseases. This review emphasized the distinction between nutritional prevention of prostate cancer as against the use of dietary or nutritional treatments for established prostate cancer. Lycopene may be particularly important in preventing small prostate cancer lesions from developing into more aggressive and lethal forms (83), which is the variant seen in African Americans. A large case-control study that demonstrated the dietary risk of animal products in black men did not show a clear association between lycopene-rich foods and prostate cancer risk (38). Our unpublished pilot data appears to suggest that African-American men in the Washington DC area consumed tomato-sauce less frequently than control African migrants, and that prostate cancer cases ate less tomato-sauce than the controls from the same population (Ukoli, F.).

Lycopene Supplement and Tomato-Sauce Diet Intervention Clinical Trials (CT):

A large body of data supports the use of tomato-products and lycopene as for chemoprevention against prostate cancer (83-85). This has warranted intervention studies to study the effect of this agent in humans. The following are abstract reports from some of such studies.

Phase I Clinical Trial:

In this trial 10mg/day of lycopene for three months reduced PSA and bone pain and increased patient performance status in 20 consecutive patients with hormone refractory prostate cancer. Between January 2001 and December 2002, 20 consecutive patients (median age 72; range 56-90) with metastatic HRPc were enrolled in the study. Lycopene in the dose of 10 mg/day was administered for a period of 3 months. Inclusion criteria were patients previously treated with hormonal therapy now with clinical and biochemical evidence of disease progression. A complete response (CR) was defined as a normalization of PSA (<4 ng/mL) and the disappearance of any sign of disease for at least 8 weeks. A partial response was defined as a >50% decrease in PSA level for at least 8 weeks associated with improvement (or no worsening) in ECOG PS and relief of bone pain if present. Stable disease (SD) was defined as a <50% decrease or <25% increase in the PSA level associated with no worsening of ECOG PS and/or bone pain for at least 8 weeks. RESULTS: One patient (5%) had complete response. Partial response was achieved in 6 (30%), disease remained stable in 10 (50%) and progressed in three (15%) patients. ECOG PS was Grade 0 in five, Grade I in 10 and Grade II in five of the 20 patients. It improved from Grade I to 0 in seven and Grade II to I in three patients. It deteriorated in three and remained unchanged in the rest seven patients. Bone pain was present in 16 (Grade 1 in six and Grade 2 in 10) of the 20 patients. Grade 1 changed to Grade 0 in five and Grade II changed to Grade 1 in five patients. Bone pain remained unchanged in 5 (31%) and worsened in 1 (6%). Ten (62%) patients managed to cut down the dose of analgesics on daily basis. Eighteen patients had associated LUTS, which improved (Q max > or = 12 mL/sec) in 11 (61%) patients. The median duration of response was 25 weeks (range 12-72 weeks). No drug intolerance or toxicity was encountered in any patient. CONCLUSIONS: Lycopene therapy appears to be effective and safe in the treatment of HRPc. It not only takes care of the rising PSA but also improves the ECOG performance status, bone pain and LUTS. Because of its relative innocuousness it should be tried before the use of more toxic substances (86).

Phase II Randomized CT:

32 Caucasian patients with localized prostate cancer consumed pasta dishes with tomato-based sauce (30 mg lycopene per day) for 3 weeks prior to prostatectomy and serum and prostate tissue lycopene levels increased, and mean PSA levels decreased (87-89).

1. The effects of consumption of tomato sauce-based pasta dishes on lycopene uptake, oxidative DNA damage, and prostate-specific antigen (PSA) levels in patients already diagnosed with prostate cancer was conducted. These data indicate a possible role for a tomato sauce constituent, possibly lycopene, in the treatment of prostate cancer.

32 patients with localized prostate cancer consumed tomato sauce-based pasta dishes for the 3 weeks (30 mg of lycopene per day) preceding their scheduled radical prostatectomy. Serum and prostate lycopene concentrations, serum PSA levels, and leukocyte DNA oxidative damage (ratio of 8-hydroxy-2'-deoxyguanosine [8-OHdG] to 2'-deoxyguanosine [dG]) were assessed before and after the dietary intervention. DNA oxidative damage was assessed in resected prostate tissue from study participants and from seven randomly selected prostate cancer patients. All statistical tests were two-sided. After the dietary intervention, serum and prostate lycopene concentrations were statistically significantly increased, from 638 nM (95% confidence interval [CI] = 512 to 764 nM) to 1258 nM (95% CI = 1061 to 1455 nM) ($P < .001$) and from 0.28 nmol/g (95% CI = 0.18 to 0.37 nmol/g) to 0.82 nmol/g (95% CI = 0.57 to 1.11 nmol/g) ($P < .001$), respectively. Compared with pre-intervention levels, leukocyte oxidative DNA damage was statistically significantly reduced after the intervention, from 0.61 8-OHdG/10(5) dG (95% CI = 0.45 to 0.77 8-OHdG/10(5) dG) to 0.48 8-OHdG/10(5) dG (95% CI = 0.41 to 0.56 8-OHdG/10(5) dG) ($P = .005$). Furthermore, prostate tissue oxidative DNA damage was also statistically significantly lower in men who had the intervention (0.76 8-OHdG/10(5) dG [95% CI = 0.55 to 0.96 8-OHdG/10(5) dG]) than in the randomly selected patients (1.06 8-OHdG/10(5) dG [95% CI = 0.62 to 1.51 8-OHdG/10(5) dG]; $P = .03$). Serum PSA levels decreased after the intervention, from 10.9 ng/mL (95% CI = 8.7 to 13.2 ng/mL) to 8.7 ng/mL (95% CI = 6.8 to 10.6 ng/mL) ($P < .001$) (87).

2. The effects of lycopene supplementation was investigated among 26 patients with clinically localized (14 T(1) and 12 T(2)) prostate cancer. These patients were randomly assigned to receive 15 mg of lycopene ($n = 15$) twice daily or no supplementation ($n = 11$) for a period of 3 weeks before radical prostatectomy. The results suggest that lycopene supplementation may decrease the growth of prostate cancer (90, 91).

Biomarkers of differentiation and apoptosis were assessed by Western blot analysis on benign and malignant parts of the prostate gland. Prostatectomy specimens were entirely embedded, step-sectioned, and evaluated for pathological stage, Gleason score, volume of cancer, and extent of high-grade prostatic intraepithelial neoplasia. Plasma levels of lycopene, insulin-like growth factor-1 (IGF-1), IGF binding protein-3, and prostate-specific antigen were measured at baseline and after 3 weeks of supplementation or observation. Eleven (73%) subjects in the intervention group and two (18%) subjects in the control group had no involvement of surgical margins and/or extra-prostatic tissues with cancer ($P = 0.02$). Twelve (84%) subjects in the lycopene group and five (45%) subjects in the control group had tumors <4 ml in size ($P = 0.22$). Diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia was present in 10 (67%) subjects in the intervention group and in 11 (100%) subjects in the control group ($P = 0.05$). Plasma prostate-specific antigen levels decreased by 18% in the intervention group, whereas they increased by 14% in the control group ($P = 0.25$). Expression of connexin 43 in cancerous prostate tissue was 0.63 ± 0.19

absorbance in the lycopene group compared with 0.25 ± 0.08 in the control group ($P = 0.13$). Expression of bcl-2 and bax did not differ significantly between the two study groups. IGF-1 levels decreased in both groups ($P = 0.0002$ and $P = 0.0003$, respectively) (90).

3. Advanced metastatic prostate cancer was treated in 54 patients randomized to orchidectomy only or orchidectomy plus 4mg daily lycopene, and the lycopene group fared better at 6- and 24-month. Adding lycopene to orchidectomy produced a more reliable and consistent decrease in serum PSA level; it not only shrinks the primary tumour but also diminishes the secondary tumours, providing better relief from bone pain and lower urinary tract symptoms, and improving survival compared with orchidectomy alone (92).

The efficacy of lycopene plus orchidectomy with orchidectomy alone in the management of advanced prostate cancer was compared in fifty-four patients with histologically confirmed metastatic prostatic cancer (M1b or D2) and a performance status of 0-2 (World Health Organization). The trial comprised two treatment arms, i.e. patients were randomized to orchidectomy alone or orchidectomy plus lycopene (OL), each of 27 patients. Lycopene was started on the day of orchidectomy at 2 mg twice daily. Patients were evaluated clinically before and every 3 months after the intervention, with measurements of prostate-specific antigen (PSA), a bone scan and uroflowmetry, with the clinical response assessed as the change in these variables. RESULTS: At 6 months there was a significant reduction in PSA level in both treatments, but more marked in the OL group (mean 9.1 and 26.4 ng/mL, $P = 0.9$). After 2 years these changes were more consistent in the OL group (mean 3.01 and 9.02 ng/mL; $P < 0.001$). Eleven (40%) patients in orchidectomy and 21 (78%) in the OL group had a complete PSA response ($P < 0.05$), with a partial response in nine (33%) and four (15%), and progression in seven (25%) and two (7%), respectively ($P < 0.05$). Bone scans showed that in the orchidectomy arm only four (15%) patients had a complete response, vs eight (30%) in the OL group ($P < 0.02$), with a partial response in 19 (70%) and 17 (63%), and progression in four (15%) and two (7%), respectively ($P < 0.02$). There was a significant improvement in peak flow rate in the OL group, with a mean difference of $+1.17$ mL/s ($P < 0.04$). Of the 54 patients who entered the trial, 19 (35%) died, 12 (22%) in orchidectomy and seven (13%) in OL group ($P < 0.001$) (92).

4. A prospective trial of lycopene supplementation was conducted to evaluate its usefulness in biochemically relapsed prostate cancer. Thirty-six men were enrolled and received escalating doses of lycopene over a one year period, they did not show any response to this treatment, but the treatment was safe and well tolerated. The plasma levels of lycopene were similar for a wide dose range (15 to 90 mg/day) and plateaued by 3 months (93).

Thirty-six men with biochemically relapsed prostate cancer were enrolled in a dose-escalating, Phase I-II trial of lycopene supplementation. Six consecutive cohorts of 6 patients each received daily supplementation with 15, 30, 45, 60, 90, and 120 mg/day for 1 year. The serum levels of prostate-specific antigen (PSA) and plasma levels of lycopene were measured at baseline and every 3 months. The primary endpoints were PSA response (defined as a 50% decrease in serum PSA from baseline), pharmacokinetics, and the toxicity/tolerability of this regimen. RESULTS: A total of 36 patients were enrolled. The median age was 74 years (range 56 to 83), with a median serum PSA at entry of 4.4 ng/mL (range 0.8 to 24.9). No serum PSA responses were observed, and 37% of patients had PSA progression. The median time to progression was not reached. Toxicity was mild, with 1 patient discontinuing therapy because of diarrhea. Significant elevations of plasma lycopene were noted at 3 months and then appeared to plateau for all six dose levels. The plasma levels for doses between 15 and 90 mg/day were similar, with additional elevation only at 120 mg/day (93).

Other Considerations:

Variation in bioavailability of lycopene across food preparation methods world wide calls for serious attention to the presentation of lycopene in supplement or whole-food form. While some cultures consume tomato-based foods cooked in olive-oil others may not. This is the basis for searching for whole-food supplements that might be easier to use in an intervention, than proposing dietary changes (94,95). Research in humans (87) and laboratory animals (96) support whole-food tomato intervention rather than single nutrient supplementation to halt or retard cancer progression.

Various biomarkers of intervention effect have been reported in several studies, but not all of them will be measured in this study. This study will focus on serum PSA (97), plasma lycopene (98,99) and plasma isoprostane (100,101). Additional markers of carcinogenic activity such as DNA damage and biomarkers of inflammation will not be addressed in this study. Samples will be collected and stored to evaluate these other biomarkers in the future.

8. Objectives.

The overall purpose of this study is to determine the format of lycopene supplement, a single nutrient (Lycopene) or whole-food tomato extract (Lyc-O-Mato®), that will best inhibit progression of biochemical relapse (PSA recurrence), among African-American men that had been treated for localized prostate cancer.

Specific objectives of the study are to:

- i. Determine the supplement, single nutrient lycopene or whole-food tomato extract, that best:
 - increase plasma lycopene levels.
 - decrease serum PSA levels.
 - decrease the biomarker of oxidative stress (F2-isoprostane).
- ii. Determine the supplement, single nutrient lycopene or whole-food tomato extract, that best:
 - impact serum androgen levels (Total & free testosterone, DHT).
- iii. Describe and compare the type and severity of adverse events associated with lycopene or tomato-extract supplementation.
- iv. Assess and compare the impact of lycopene and tomato-extract supplementation on quality of life (QOL) scores among the prostate cancer survivors in the intervention study.

Hypotheses / Predicted outcomes of the study.

Null Hypothesis: H_0

There is no difference in the ability of lycopene supplementation from single nutrient lycopene (Arm-A), or lycopene from a tomato-extract supplement Lyc-O-Mato® (Arm-B), to impact plasma lycopene, and inhibit progression of PSA recurrence as measured by inhibition of rise in serum PSA, and F2-isoprostane, the biomarker of oxidative stress.

Alternative Hypothesis: H_A

Lycopene from tomato-extract (Arm-B) will be more efficient in the inhibition of prostate cancer progression than single nutrient lycopene (Arm-A) among African-American men who are presenting with PSA recurrence after previous adequate response to treatment for localized prostate cancer.

- | | |
|--|---------------|
| -Post-intervention mean plasma lycopene: | Arm-B > Arm-A |
| -Post-intervention mean serum PSA: | Arm B < Arm-A |
| -Proportion of men with Complete Response: | Arm-B > Arm-A |
| -Proportion of men with improved QOL scores: | Arm B > Arm A |
| -Mean biomarker of oxidative stress: | Arm B < Arm-A |

9. Study Population.

a. Target population:

The study target population to whom the results can be generalized will be African-American that had been successfully treated in the past for localized prostate cancer by radical prostatectomy, external beam radiation, brachytherapy, or androgen withdrawal therapy, and are currently presenting with biochemical relapse, PSA recurrence. Study participants will be recruited from among patients who reside in Tennessee. The annual incidence of prostate cancer among African-American men in TN from 2000 – 2005 averaged 108 cases, ranging from 86-122 cases per year, and a projected 30% of prostate cancer survivors might develop biochemical failure after 15 – 20 years of diagnosis. In a review conducted in 1994, there were 431 men seen at the VUMC with PSA recurrence, and 24 (5.5%) were African-American. This number will be slightly higher now that prostate cancer patients seen at Meharry are referred to VUMC, and those from the VA are also managed at VUMC. Currently over 200 patients are diagnosed annually at the VUMC with prostate cancer, of which 10-15 will meet the study eligibility criteria.

b. Methods.

In this clinical trial we propose to use a convenience sample of study eligible men who volunteer to participate in the study. Prostate cancer patients identified through the TN cancer register and through urologists' offices, who have self-identified themselves as African-American in their records, will be contacted by mail, and invited to consider participation in the study. The study will be restricted to men who reside in Tennessee (Nashville and surrounding counties in particular), and presenting with PSA recurrence after successful treatment for organ-confined prostate cancer. The study brochure will be displayed at the urology clinics of the VUMC and MMC, Urology Associates, Nashville, a major urology office of over 25 urologists, and the office of William Hughes, M.D., an African-American Urologist in Nashville.

To be included in this study the participant will have to be male, at least 40 years, and self-identified as African-American/Black. They also must be presenting with PSA recurrence after successful treatment for localized prostate cancer in the past. Exclusion criteria include enrolment in an overlapping intervention study, life-expectancy of less than one year, hormone or chemotherapy within the preceding 4 weeks. (See below for more details for inclusion/exclusion criteria)

The study sample size has been estimated at 78 men, 39 participants for each study arm, setting an alpha of 0.05, power of 80%, and a conservative PSA slope reduction of 30%, for a 12-month intervention period. Anticipating a 15% drop-out rate, we plan to enroll up to 90 study-eligible patients into the study.

Exclusion from the study on the basis of demographic characteristics are for valid reasons:

- Females cannot be in this study because they do not suffer from this condition.
- Men younger than 40 years have been excluded because biochemical PSA recurrence will be very rare in men under the age of 40 years, given that prostate cancer is rare under the age of 40 years.
- African-Americans record the highest incidence and mortality rate for prostate cancer in the world, and this study is intended to specially target this high risk population, and identify any intervention that might retard prostate cancer progression.
- Other ethnic groups have been excluded for the following reasons:
 - Prostate cancer is very rare in Asians and American-Indians, and so it will be very difficult to find men who meet the study eligibility criteria in the Nashville area.
 - A similar study has already been conducted among white men, and in that study only 2 African-Americans were recruited.

10. Protocol Design:

This is a two-arm randomized intervention study that will not have a placebo group as both study arms will be receiving one of two forms of the dietary supplement, lycopene.

a. Subject Identification: Code system:

Potential study participants will be identified from:

- i) Urologist/Oncologist office
- ii) The Community
- iii) TN Cancer Register

At recruitment study participants will receive a study identification number when they register with the study. Their name will appear only on the personal information questionnaire. This questionnaire will be stored separate from other study questionnaires. A study register will be maintained that will include their names and the equivalent study identification numbers. This study identification number, not their names, will appear on all other study questionnaires, stored samples, laboratory and pathology reports, and samples that will be sent out to laboratories. All questionnaires and samples will be dated at the time of collection. Data collected in this study will be entered into a database as collected, such that at completion of all data entry, an electronic file that includes names and identification numbers will be created and saved separate from the rest of the study database that will carry their study identification number, but not the names of participants. In this way the identity of participants will be protected and cannot be traced from the study database or their samples.

The study identification number will be made up of a 3-digit number with a three-alphabet prefix LCT (Lycopene Clinical Trial) starting at LCT501 to LCT599 such that patients will be assigned consecutive ID numbers as they are recruited within each Gleason score strata as indicated below:

Gleason Score < 8	LCT501 – LCT550
Gleason Score 8-10	LCT551 – LCT600

Numbering has been arranged separately for both strata to facilitate the process of randomization within each strata, and extra registration numbers have been made available within each strata to accommodate over 15% drop-out rate.

b. Description of the Recruitment Process.

(1) Participant Availability

Prostate cancer patients are followed up by their urologist or oncologist four or more times a year, and each visit to the doctor is an opportunity to give them information about ongoing clinical trials for which they might be interested and eligible. Men with PSA recurrence will be seen more frequently, and since this study does not exclude any other form of treatment by the urologist, a high proportion of eligible patients are expected to be interested. It is also logistically possible to schedule study visits to coincide with regular urologist visits for MMC and VU patients.

(2) Inclusion & Exclusion Criteria

This study will be restricted to African-American men who are 40 years and older residing in Tennessee.

Inclusion criteria:

- i) Had been diagnosed with prostate cancer, and had responded to treatment by radical prostatectomy or radiation (seed implantation or external beam radiation), or

- hormone withdrawal treatment.
- ii) Currently presenting with biochemical relapse or PSA recurrence defined according to initial treatment:
- Men who had radical prostatectomy:
Two successive PSA rise at least one month apart, or PSA >0.2 ng/ml, after initial fall to undetectable level.
 - Men who had radiation treatment:
Two successive PSA rise at least one month apart, above the lowest value attained (nadir) after radiation.
 - Men who had hormone treatment:
Two successive PSA rise at least one month apart, above the lowest value attained after hormonal treatment.

Exclusion criteria:

- i) Enrolled in an overlapping intervention.
- ii) Taking supplements containing lycopene.
- iii) Taking any micronutrient supplements containing doses greater than the US RDA for each vitamin, mineral, or micronutrient.
- iv) Life-expectancy less than 1 year by clinician recommendation.
- v) Mental incompetence
- vi) Indication of erratic lifestyle that may interfere with compliance or follow-up
- vii) Hormone or chemotherapy within the past 4 weeks.

(3) Methods for Recruiting, Retention, and Follow-up

Recruiting:

Prostate cancer survivors with biochemical failure will be recruited from three main sources, the urologist/oncologist office, the cancer register, and from the community as follows:

i) Urologist/Oncologist office

Urologists/oncologists who care for patients who might be eligible for this study will be approached with the details of the study to see if they will allow study brochures to be displayed in their office. Eligible patients will be informed that this study does not replace their primary treatment choice, and that the study supplement has not been guaranteed to cure biochemical failure. Interested men will be asked to contact the clinical trial study personally.

Urology and oncology offices that will be contacted in Nashville will include Meharry Medical College, Vanderbilt University Medical Center, Veterans Hospital, Urology Associates P.C, and the office of William Hughes, M.D.

ii) TN Cancer Register

The cancer register does not capture the diagnosis of biochemical failure. However the registry captures all men diagnosed with prostate cancer, and such a listing can be obtained from the Tennessee state cancer register for those diagnosed 5 or more years ago. Study brochures and letters of invitation to participate in this study will be mailed to each person on the register. Interested patients will be asked to contact the study clinic to arrange to participate in the study. Patients will be asked to inform their urologist about their choice to participate, and with their permission the study PI will then inform the patient's urologist about the study to solicit their cooperation. This will be particularly important in the instance of urologists who are not aware of the study, and those that are not listed in the section above.

iii) Community

The public media, particular the health calendar of two local newspapers, will be utilized to advertise this study. More specifically religious organizations, fraternities & associations, recreation

centers, and senior citizens centers will also be sites where study flyers will be displayed. Local prostate cancer support groups such as the UsTOO® International, and the ‘Man-To-Man’ of the American Cancer Society will also be contacted to provide a forum for their members to listen to a presentation about the study, and for the distribution of study brochures.

Retention:

This study plans to optimize retention by ensuring adequate education of all potential participants from the onset. They will be reassured that successful participation in a clinical trial can be a challenge, and that a certain amount of compliance is required if the study results are to be meaningful. The study team understands such problems and each participant will be encouraged to call and inform the nurse/coordinator or the PI about any difficulties they are facing, so that the situation can be addressed immediately and effectively. They will be made to understand that the members of the team are available to support them to remain in the study until its conclusion.

From the onset participants will be told that we realize that the study cannot afford to pay for their time, and that we are not trying to do that. However we plan to show respect of their time by the offer of a cash incentive to at least offset the cost of transportation, parking, and the inconvenience of blood draw. In addition, this second strategy to encourage retention will include the provision of study gifts at each visit, such that the gifts are pro-rated to maintain their interest. The first gift at enrolment will be a T-shirt with the study logo, and the gift at study conclusion will be a framed certificate of appreciation with a pin to commemorate the activity. All other study follow-up time points will be celebrated with the presentation of assigned study gifts like pens and mugs.

The third strategy to ensure retention is to form a close bond, and to win the trust of the participants by keeping in contact with them by telephone and at their urologist/oncologist office. The responsibility to monitor compliance will rest mainly with the nurse/coordinator at both study sites. The study plans follow-up calls to monitor compliance and adverse events weekly in the first month, bi-weekly in the second month, and once a month there after. In addition the PI will also make one call each month to greet participants, and to thank them for their continued participation. At this call the PI will inform them about study accrual and study progress. All participants will also be encouraged to call the study numbers whenever they feel like doing so.

Follow-up:

At recruitment contact information (telephone and home address) will be collected, such that participants can be reached by telephone or by mail. All 7 study visits will be scheduled three months apart at recruitment, a copy placed in the study records, a second copy in their medical records, and a third copy for the participant’s record. Participants will receive a call at the end of the second month to find out if the scheduled date is still convenient. In case of any conflict participants can arrange to reschedule within a 2-week interval before or after the planned visit date. They will receive a reminder in the mail 1 week to the scheduled visit, and a call the day before the visit. A missed visit can be rescheduled as soon as possible but not later than 4 weeks, and all remaining visits scheduled 3 months apart from that date. The records on file will be updated and the participant will receive a new schedule of visits. If the missed-visit cannot be made-up within 4 weeks, then that time-point will be treated as ‘missed’ and the subsequent scheduled visit is retained as planned. A protocol to this effect is attached.

While scheduling study visits will be the responsibility of the nurse/coordinators at both sites, the research assistant will be responsible for sending out reminders, and rescheduling when necessary. This way follow-up calls and scheduling calls will be handled separately.

- (4) Data to support recruitment and retention estimates:

This will be the first clinical trial to be conducted by this PI in Nashville. However other investigators in the group, Jay Fowke (2 studies listed) and Omer Kucuk (3 studies listed), have been involved in other successful clinical studies, and they will bring their experience to this study.

Effects of Brassica on Markers of Colon Cancer Risk” (NCI CA95791; PI: J. Fowke; Project Coordinator: S. Motley). This was a randomized, crossover trial investigating the effects of Brassica consumption on colorectal cancer biomarkers. Toward this 3-month trial, we successfully recruited 40% of identified and eligible adenoma patients to reach our target (20 adenoma patients. 14 men, 6 women). No participants dropped-out or were lost to follow-up. After obtaining informed consent, each participant completed a run-in trial, a Brassica diet intervention, and a multivitamin supplement intervention. Data were collected at baseline and after each intervention (i.e., 3 data collections), and included fasting, first-morning urine specimens, a one time buccal cell sample, and a rectal biopsy. This biopsy procedure involved inserting a small tube into the rectum to a depth of 2-4 inches, and 6 to 8 small pinches of tissue approximately 1 mm thick were procured. We also measured each participant’s weight, height, hip and waist circumference, and each participant completed a questionnaire to monitor for adverse events. Participants also talked to the Project Coordinator during scheduled telephone calls before and after each clinic visit. We also administered a total of nine 24-hour diet recall telephone interviews over the three month period, and participants completed two food diaries and attended three nutrition education classes. During the diet intervention, participants were asked to increase Brassica intake using the food preparations taught in the classes, and participant Brassica intake averaged 220 grams/day (> 2 servings/day) during this intervention.

Effects of Brassica or indole-3-carbinol on Prostatectomy Patients with PSA Recurrence (American Institute of Cancer Prevention; PI: J. Fowke; Project Coordinator: S. Motley). This is a 3-armed, placebo-controlled, randomized trial to evaluate the effects of Brassica intake or indole-3-carbinol (I3C) supplementation on PSA levels among prostate cancer survivors. Eligible men had undergone a prostatectomy for prostate cancer and since had experienced biochemical failure and PSA recurrence. Of the 16 eligible patients identified, 15 (90%) consented to participate in this 6 month trial. At this time, all 15 have completed the intervention. Men who agreed to be in the study were asked to do the following over a six month time period. During the trial, participants agreed to visit our study center five times and provide a first-morning urine specimen, a fasting sample of blood, completed a follow-up questionnaire, and permit measurement of weight, height, hips and waist circumferences. We also administered a total of 12 24-hour diet recall interviews over the 6 month intervention, and participants completed two food diaries. The Project Coordinator calls each participant at scheduled intervals to monitor for adverse events.

Soy isoflavones in the treatment of prostate cancer. Nutr Cancer. 2003;47(2):111-7.

Hussain M, Banerjee M, Sarkar FH, Djuric Z, Pollak MN, Doerge D, Fontana J, Chinni S, Davis J, Forman J, Wood DP, **Kucuk O**.

To determine the clinical effects of soy isoflavones on Pca we conducted a pilot study in patients with Pca who had rising serum prostate-specific antigen (PSA) levels. Patients with Pca were enrolled in the study if they had either newly diagnosed and untreated disease under watchful waiting with rising PSA (group I) or had increasing serum PSA following local therapy (group II) or while receiving hormone therapy (group III). The study intervention consisted of 100 mg of soy isoflavone (Novasoy) taken by mouth twice daily for a minimum of 3 or maximum of 6 mo. Forty-one patients were enrolled (4 in group I, 18 in group II, and 19 in group III) and had a median PSA level of 13.3 ng/ml. Thirty-nine patients could be assessed for response. Soy isoflavone supplementation was given for a median of 5.5 (range 0.8-6) mo per patient. Although there were no sustained decreases in PSA qualifying for a complete or partial response, stabilization of the PSA occurred in 83% of patients in hormone-sensitive (group II) and 35% of hormone-refractory (group

III) patients. There was a decrease in the rate of the rise of serum PSA in the whole group ($P = 0.01$) with rates of rise decreasing from 14 to 6% in group II ($P = 0.21$) and from 31 to 9% in group III ($P = 0.05$) following the soy isoflavone intervention. Serum genistein and daidzein levels increased during supplementation from 0.11 to 0.65 microM ($P = 0.00002$) and from 0.11 to 0.51 microM ($P = 0.00001$), respectively. No significant changes were observed in serum levels of testosterone, IGF-1, IGFBP-3, or 5-OHmdU. These data suggest that soy isoflavones may benefit some patients with Pca.

Effects of lycopene supplementation in patients with localized prostate cancer. Exp Biol Med. (Maywood). 2002; 227(10):881-5. **Kucuk O**, Sarkar FH, Djuric Z, Sakr W, Pollak MN, Khachik F, Banerjee M, Bertram JS, Wood DP Jr.

A clinical trial to investigate the biological and clinical effects of lycopene supplementation in patients with localized prostate cancer. Twenty-six men with newly diagnosed prostate cancer were randomly assigned to receive a tomato oleoresin extract containing 30 mg of lycopene ($n = 15$) or no supplementation ($n = 11$) for 3 weeks before radical prostatectomy. Biomarkers of cell proliferation and apoptosis were assessed by Western blot analysis in benign and cancerous prostate tissues. Oxidative stress was assessed by measuring the peripheral blood lymphocyte DNA oxidation product 5-hydroxymethyl-deoxyuridine (5-OH-mdU). Usual dietary intake of nutrients was assessed by a food frequency questionnaire at baseline. Prostatectomy specimens were evaluated for pathologic stage, Gleason score, volume of cancer, and extent of high-grade prostatic intraepithelial neoplasia. Plasma levels of lycopene, insulin-like growth factor-1, insulin-like growth factor binding protein-3, and prostate-specific antigen were measured at baseline and after 3 weeks of supplementation or observation. After intervention, subjects in the intervention group had smaller tumors (80% vs 45%, less than 4 ml), less involvement of surgical margins and/or extra-prostatic tissues with cancer (73% vs 18%, organ-confined disease), and less diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia (33% vs 0%, focal involvement) compared with subjects in the control group. Mean plasma prostate-specific antigen levels were lower in the intervention group compared with the control group. This pilot study suggests that lycopene may have beneficial effects in prostate cancer. Larger clinical trials are warranted to investigate the potential preventive and/or therapeutic role of lycopene in prostate cancer.

Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. Cancer Epidemiol Biomarkers Prev. 2001 Aug;10(8):861-8. **Kucuk O**, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F, Li YW, Banerjee M, Grignon D, Bertram JS, Crissman JD, Pontes EJ, Wood DP Jr.

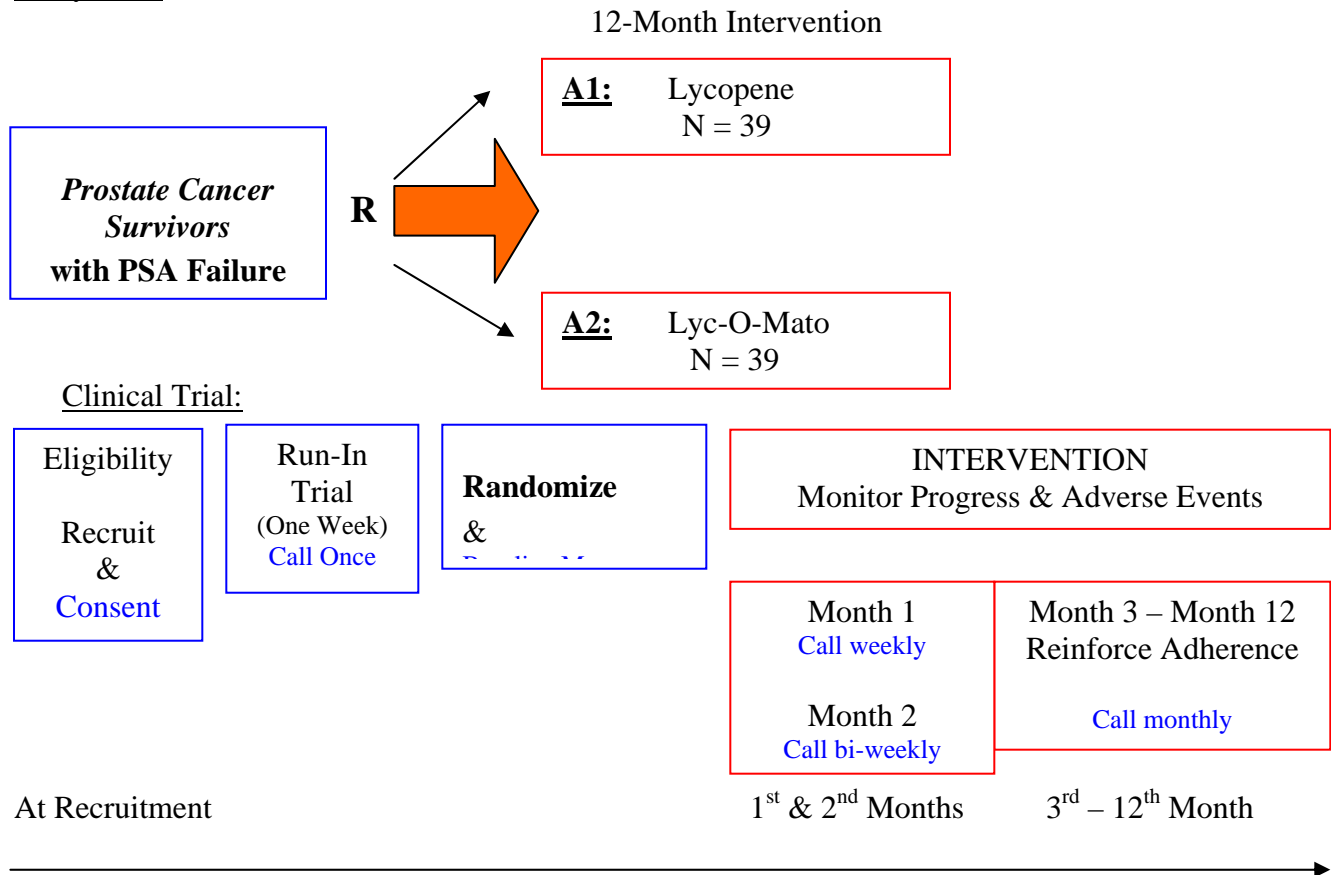
Twenty-six men with newly diagnosed, clinically localized (14 T(1) and 12 T(2)) prostate cancer were randomly assigned to receive 15 mg of lycopene ($n = 15$) twice daily or no supplementation ($n = 11$) for 3 weeks before radical prostatectomy. Biomarkers of differentiation and apoptosis were assessed by Western blot analysis on benign and malignant parts of the prostate gland. Prostatectomy specimens were entirely embedded, step-sectioned, and evaluated for pathological stage, Gleason score, volume of cancer, and extent of high-grade prostatic intraepithelial neoplasia. Plasma levels of lycopene, insulin-like growth factor-1 (IGF-1), IGF binding protein-3, and prostate-specific antigen were measured at baseline and after 3 weeks of supplementation or observation. Eleven (73%) subjects in the intervention group and two (18%) subjects in the control group had no involvement of surgical margins and/or extra-prostatic tissues with cancer ($P = 0.02$). Twelve (84%) subjects in the lycopene group and five (45%) subjects in the control group had tumors <4 ml in size ($P = 0.22$). Diffuse involvement of the prostate by high-grade prostatic intraepithelial neoplasia was present in 10 (67%) subjects in the intervention group and in 11 (100%) subjects in the control group ($P = 0.05$). Plasma prostate-specific antigen levels

decreased by 18% in the intervention group, whereas they increased by 14% in the control group ($P = 0.25$). Expression of connexin 43 in cancerous prostate tissue was 0.63 ± 0.19 absorbance in the lycopene group compared with 0.25 ± 0.08 in the control group ($P = 0.13$). Expression of bcl-2 and bax did not differ significantly between the two study groups. IGF-1 levels decreased in both groups ($P = 0.0002$ and $P = 0.0003$, respectively). The results suggest that lycopene supplementation may decrease the growth of prostate cancer. However, no firm conclusions can be drawn at this time because of the small sample size.

(5) Participants assignment to experimental groups and methods of randomization:

This is a 2-arm, double-blind, randomized study. There will be no placebo group in this study as we want participants to benefit from any prostate cancer protective action of lycopene. The study participants and the investigators will be blinded as to the intervention that is received, while the pharmacist who will randomize the patients, and be the custodian of the study intervention code, will not be a study investigator. Details of the randomization process is presented in sub-section e.

Study Plan:



(6) Study endpoints:

Primary Clinical Endpoints:

- PSA response to supplementation, defined as a minimum of 50% reduction from baseline PSA maintained for 2 successive readings 3 months apart.
- Duration in months of maintenance of PSA reduction from baseline values.

Secondary Clinical End-Points:

- QOL response to supplementation, defined as $> 25\%$ improvement in QOL scores.
- Occurrence and extent of distant metastasis. (X-ray and Bone scan changes)

Primary biomarker endpoints:

- a) Changes in plasma lycopene
- b) Changes in biomarker of oxidative stress: 8-isoprostane-PGF_{2α}

Secondary biomarker endpoints to be measured in future study:

- a). Changes in DNA oxidation product: 5-OHmdU
- b). Changes in biomarker of inflammation: IL-6

While lycopene is expected to act directly by reducing oxidative stress as measured by isoprostane, it will be useful to also evaluate how lycopene affects other biomarkers that are associated with carcinogenesis, such as DNA oxidation products and measures of inflammation. Blood samples will be stored appropriately to measure both of these secondary endpoints in a future study.

Intermediate biomarker endpoints:

- a). Testosterone: Free, Total and DHT
 - b). Plasma IGF-1 and IGFBP-3 (Future study)
- Intermediate end-points will be useful in the determination of the mechanism by which

lycopene modulates PSA. Male hormones will be assessed in this study, but blood samples will be stored to measure IGF-I and related biomarkers in a future study.

Response definitions:

Complete PSA response (CR):

- i) Normalization of PSA to undetectable levels for 2 successive determinations a minimum of 3 months apart among patients who had radical prostatectomy.
- ii) Normalization of PSA to nadir value sustained for 2 successive determinations a minimum of 3 months apart among radiotherapy patients.

Partial response (PR):

At least 50% reduction from baseline PSA, short of normalization, sustained for at least 2 successive determinations a minimum of 3 months apart.

Progressive disease (PD):

At least 50% increase from baseline PSA, or the minimum PSA level observed during the study, sustained for two successive determinations a minimum of 3 months apart.

Stable disease (SD):

Does not qualify for CR, PR or PD, with PSA remaining as at the time of randomization, including a less than 50% decrease or increase from baseline levels.

Duration of Response: Duration in months from the first time a complete response or partial response is noticed until the time of disease relapse or progression indicated as a rise in PSA to pre-response level and higher.

Time to Treatment Failure: Duration in months from date of randomization to the date of disease progression, or to the date taken off-treatment due to any reason including toxicity, or to the date of refusal to continue in the study, or to the date of death.

c. Description of the informed consent process.

Information about study rationale:

Potential study participants will be told by the study coordinator, that this study to investigate the usefulness of lycopene nutrient supplementation in the complementary management

of biochemical relapse (PSA recurrence) among African-American prostate cancer survivors is a clinical trial. Although lycopene is already on the market for its favorable effect on prostate health, there is still an urgent need to authenticate such claims. Such a study will be extremely expensive because of the required very large number of healthy men, and the long duration of several years that will be required to successfully conduct such a study. Conducting the study in men already diagnosed with prostate cancer will require much fewer men, and possibly much shorter study duration. Participants will be informed that this nutrient supplement is being tried as an addition to the treatment that their urologist/oncologist will be planning with them, and is not meant to replace such treatment plans. They will receive a reference listing of previous lycopene intervention studies, a summary of the findings of such lycopene trials, a full description of all the procedures in this clinical trial, the duration of the intervention, and the number of visits required to complete the study.

Information about study procedure:

They will also receive information about what will be expected of a participant at each visit, the benefits and risks of the intervention, and the fact that all study information will be held in strict confidence. They will be told that they have the right to refuse to participate or withdraw from the clinical trial at any time without any sanctions, and that refusal to participate, or withdrawal from the study, will not affect their treatment plan with their urologist/oncologist, or their health insurance coverage in any way. Potential participants will be encouraged to only consent after discussing with their family members, close friend, and their physician. It will be explained that this study will be measuring PSA (free and total), lycopene, isoprostane and testosterone (free and total) at this time, and that portions of the blood samples collected will be stored for additional laboratory analysis at a later date. These secondary analysis will not affect the results of the current study, but will be extremely useful in determining the mechanism by which lycopene is able to affect PSA levels and inhibit prostate carcinogenesis.

Information about the study supplement:

In addition participants will receive explanation about the difference between lycopene single nutrient, and lycopene from the tomato-extract Lyc-O-Mato®, the process of randomization, and the 'double-blind' nature of the study. It will be emphasized that both the study participants and the study investigators will not know which form of the lycopene supplement each participant will be receiving. Participants will be told that this clinical trial is not trying to pay them for participating, and that the cash incentive provided is to part offset their transportation cost to the several study related visits, and that the study related gifts they will receive is in appreciation of their time and patience in making themselves available for this study for which definitive curative benefit is not assured. Participants will be told that the study coordinator will call them regularly to monitor the occurrence of any adverse event, and that they must report any adverse event to the study PI (Flora Ukoli) and/or the study coordinators immediately (Saundra Motley for patients recruited through VU, and Lavenia Crutcher for patients recruited through MMC). Participants will be informed that a physician titled the medical monitor, who is not an investigator on this study, has been appointed to ensure that any adverse event experienced by any of them will be reviewed in detail to ensure the protection of all participants. They will also be instructed that while the study will like to receive the report regarding an adverse event as soon as one occurs, participants can make this report at their convenience since they need to report to an emergency room of choice for immediate care, and depending on the severity of the adverse event they should not wait to report the event to the study staff before seeking urgent medical care.

Eligibility determination & Consent process: Provision of privacy and time to decide:

Potential study participants will be informed about the study by any of the following: study nurse/coordinators, patients' urologist/oncologist, the study PI, research assistant, by mail, and through mass media advertisement. Eligibility determination will be conducted by the study coordinators by reviewing patients' records and by interview. This interview will be conducted in-person or by telephone. The informed consent interview will be conducted by the study nurse/coordinator in-person, and will be conducted no less than 48 hours after the administration of any mind-altering substances such as tranquilizers, conscious sedation, or anesthesia and no less than two weeks after the diagnosis of biochemical failure. Potential participants will be interviewed in a private interview room designated for the purpose, will be allowed to read the consent form at their own speed (about 30 minutes), and they can consent after having all their questions answered by the nurse/coordinator, the PI, or their urologist/oncologist. They will be encouraged to discuss participation with their physician/urologist, or any other person of their choice before consenting. Delaying consent for up to 12 months will not deter recruitment into this study, so long as the participant remains eligible for the study.

Informed Consent forms:

Two additional copies of the signed informed form will be made such that one will be given to the study participant for their record, and the second will be retained in their medical record. The original informed consent will be kept with the principal investigator's study records.

Confidentiality & Privacy of Medical and Research Records

The following information will be abstracted from the medical records of participants:

- i) Prostate cancer and biochemical failure diagnosis, Gleason score and PSA at diagnosis, PSA levels, body weight, CMP, and clinical symptoms for the previous 12 months.
- ii) Reports of x-rays and scans at and since diagnosis, including the previous 12 months.
- iii) History of medical conditions and current medications.

This research will be HIPAA compliant because only patients who sign the hospital HIPAA form, which includes consent to have their medical records released for related research activities, can participate. All participants will also be asked to read and sign the study HIPAA form (copy attached). This document describes how we shall protect their information, and it also includes a list of other persons with whom we may share this information if the need arises. All members of the research team will undergo human subject protection training that includes how to confidentially handle research and medical records information of study participants.

d. Plan for Addressing Human Subject Protection Requirements

Training:

Members of this research group already have certification in the area of Human Subject Protection, and will continue to undergo continued education in this area. New staff hired for this project will also be trained and certified before taking over any study related responsibilities. Accredited online training is readily available both at Meharry Medical College, and at Vanderbilt University Medical Center.

Infrastructure:

Both institutions already have in place systems for handling the medical records of patients

confidentially. Medical records are stored electronically and in hard copies such that only authorized personnel can gain access. File cabinets with locks are available in the PIs office to store all study records, and the study electronic database will be password protected. Only research personnel will have access to these files, and only for research related activities. HIPPA forms completed by patients do include provision to release their records for research purposes. However this study still provides a study HIPPA form for participants to sign, reinforcing the fact that information from their medical records and their research records will be handled in strict confidence, and will only be available for listed activities. (HIPAA forms attached).

Safety:

The clinical trial drug is a dietary supplement that has not been reported to be unsafe for human consumption. Since the safety of research participants is extremely important, and the possibility of adverse events cannot be ruled out, a systematic plan to monitor, and handle adverse events has been put in place. A medical monitor who is external to this study has been identified to evaluate any adverse event that should occur, and protect study participants by immediately halting the study if necessary.

e. Subject Assignment: (Randomization)

This is a 2-Arm, double-blind, supplement intervention study. Recruiting men, particularly African-American men, into clinical trials can be a challenge; therefore it will be advantageous to use a randomization strategy that will ensure similar number of patients, and similar distribution by an important characteristic of disease severity, into both study arms all through the study period. We plan to stratify eligible patients by prostate cancer grade at diagnosis (Gleason score) to make both study arms as balanced as possible, and to recruit the men in blocks of patients to ensure equal numbers in both study arms. At the close of the study, or even if the study was to be halted, there will be similar numbers, and similar patient distribution by disease severity in both study arms, making for unbiased and meaningful comparison of treatment effects.

1. Blocking will be used to ensure close balance of the number of participants in each group at any time during the study such that after every block the number of participants in each group would be equal. Because blocking tends to reduce the unpredictability of randomization, we plan to use random block sizes of 4 or 2 patients per block throughout the study.
2. Stratification by Gleason score at diagnosis is desirable to ensure that the participants receiving each intervention are closely balanced by cancer grade. Randomization will be conducted separately for patients with Gleason score 7 and below, and for those with Gleason score 8 and higher. The number of study participants in either stratum cannot be predetermined, as this will depend on the distribution of cases by Gleason score in the population, and the rate of volunteering to participate in the study within each stratum. It will be assumed that response rate will be independent of Gleason score.
3. Blinding participants will be achieved by producing study supplements that look identical. Lyc-O-Mato® will be provided by the makers, and they will also provide the identical capsules that will be used to constitute the single nutrient lycopene supplement. The pharmacy at Meharry will arrange for this to be done professionally to meet the desired pharmacy standards.

The pharmacist will prepare 100 prescription dispensing containers (labels, envelopes) that have been numbered with 3-digit numbers from 101 – 200, and will maintain a register of the content of each dispensing container. The appropriate supplement will be placed in the container only after the pharmacist has completed the randomization process. The containers will be dispensed

consecutively starting from the first container, number 101. Randomization will be conducted by the pharmacist within each of two the two strata, and in blocks of 2 or 4 men, such that half of the ID numbers (men) in each block will be assigned to Arm-A and the other half to ARM-B. The corresponding supplement container (envelope) will be assigned to each study ID number, and will be dispensed as patients are recruited. The participants and investigators will be ‘blinded’, such that participants will not know the type of supplement they are receiving, the study coordinators and investigators will not know what each participant is on, but the pharmacist will be the only one who knows, and will be aware of the type of supplement in each dispensing container, and will be in possession of the code. The pharmacist is not a study investigator, will not be involved in any study activities except to randomize the participants.

Example:

Investigator’s List

Participant ID	Supplement #
LCT501	101
LCT502	102
LCT503	103
LCT504	104
LCT505	105
LCT506	106
LCT507	107
LCT508	108

Pharmacist’s Code

Supplement #	Study ARM
101	B
102	A
103	A
104	B
105	B
106	B
107	A
108	A

There are three major potential biases in this protocol. The first bias is that of self-selection to participant in the study. It is recognized that patients who are willing to take part in intervention studies are more health conscious, have more positive attitudes to the agent being studied, and may therefore end up with better clinical outcomes. This study will not control for this bias, but it is possible to develop a study of outcome differences between study participants and those who did not volunteer for the study from case record information. This study has been designed to compare the action of two forms of the same antioxidant, and since the participants are ‘blinded’, the internal bias has been addressed. Also the investigator bias has been addressed by ensuring that they too are ‘blinded’.

The second potential bias is the confounding effect of other protective nutrients (such as tocopherol) or cancer promoting nutrients (such as fatty-acids) in their diet, and even other supplements with antioxidant effects that participants may consume intentionally. This study will utilize statistical methods to control for the effect of such extrinsic nutrient intakes that will be assessed from the information collected by the Block FFQ both at the onset and end of the intervention, and by three sets of 24-hour dietary recalls at each follow-up time-point. It is more accurate to measure exposure to nutrients by laboratory blood analysis, and as such fatty-acid exposure will be measured in the laboratory. However due to financial constraints an important antioxidants such as tocopherol will be measured in a future study from samples that will be stored.

Cancer grade and stage are very important variables in the outcome of cancer treatment. The study will control for cancer grade at diagnosis by randomizing patients separately for those with Gleason score 7 and lower, and those with Gleason score 8 and higher. Information about cancer stage will be abstracted from the medical records and statistical methods will be used to address them.

f. Subject Screening Procedures (Eligibility determination)

Eligibility to participate in this study will be conducted when a participant shows interest in the study. This can happen as a telephone interview if the participant called the study number, or as a face-to-face interview if they walked-in. (Copy of script attached). Eligibility to participate will depend on a positive answer to the answer to the following questions:

Gender:	Male
Residency:	Nashville or surrounding county
Age:	40 years and older
Ethnicity:	African-American or African
Supplementation:	Not currently on any nutritional supplement other than regular multivitamin, without lycopene.
Prostate Health:	Prostate cancer diagnosis status: Confirmation that they had received and responded well to treatment (radical prostatectomy or radiation) for localized prostate cancer, and have now presented with rising PSA.
Treatment choice:	Not currently enrolled in other clinical trials.

The eligibility criteria for this study will be read to callers, and the caller will be asked if he thinks he is eligible. If the caller thinks he is eligible he will then be scheduled to report to MMC clinical trial office to be screened for study eligibility, to sign the consent form if he is confirmed to be eligible, and then to participate in the study. Names and contact information will not be collected on the telephone. Walk-in patients who are eligible and interested in the study will be requested to undergo a two-stage consent process, sign consent to be contact at a later date to schedule a study visit. At this time they will provide their name and telephone number on the form that they will sign. When they register for the study proper they will be expected to sign a full consent for the study.

g. Data Collection and Handling Procedures

Research participants will undergo the following procedures:

Initial contact:

- 1 Approached, and study introduced.
- 2 Eligibility determination conducted, with initial consent to re-contact if eligible.
- 3 Informed consent process implemented for eligible participants.

First Study Visit:

- 4 Complete study questionnaires / baseline physical measurements
- 5 Run-In Trial
- 6 Baseline fasting blood-draw, Collection of urine sample
- 7 Randomized into Study Arm-A or Study Arm-B
- 8 Receive study supplement package to last 3 months, to be replenished quarterly for a total of 12 months.

Subsequent Study Visits:

- 9 4 Follow-up visits every three months for 12 months.

Schedule of study evaluations:

Laboratory & Other Measures	Data Collection Time Line				
	Baseline Studies	Follow-up Time-Points (Month)			
		3	6	9	12
Clinical Symptom/QOL Assessment	X	X	X	X	X
Body-fat measures	X	X	X	X	X
Dietary Assessment (BLOCK FFQ)	X				X
Three 24-Hour Dietary Recall	X	X	X	X	X
Lycopene & Vitamin E	X	X	X	X	X
8-isoprostane-PGF _{2α}	X	X	X	X	X
Serum PSA (Free & Total)	X	X	X	X	X
Fatty-acids	X		X		X
Testosterone (Free, Total, DHT)	X	X	X	X	X
Comprehensive Metabolic Panel (CMP)	X	X	X	X	X
X-rays and Scans (Abstracted from Medical Record)	X	As clinically available			

Data collection:

Study visits will be scheduled in the morning between 7.30am – 10.00am so as to obtain fasting blood and urine samples. To accommodate participants' schedules, visits can be scheduled later in the morning or afternoon to collect questionnaire information for up to one hour, in addition to 15-minute supplementary visit between 7:30am – 10:00am to collect fasting blood and urine samples. Blood samples will be transferred to the laboratory where they will be processed according to the protocol, and stored until analyzed.

First study visit (1 hour)

i) Personal and medical information, including clinical symptoms, will be collected by a self-administered questionnaire. Assistance will be provided by research staff if requested. Other laboratory, x-ray, bone scan, prostate biopsy, surgical specimen information, and treatment information will be abstracted from the medical records.

ii) Quality of Life (QOL) questionnaire will be self-administered, and assistance will be offered as requested or necessary.

iii) Dietary assessment (BLOCK FFQ) is to be self-administered by participants. Total calories, total and saturated fats, lycopene, selected fatty acids, and other micro- and macro-nutrient intake will be estimated from the BLOCK FFQ by Nutritionquest, the nutrition company of the Block Dietary Data Systems. The estimated values of lycopene and other nutrient intake will subsequently be imported into the Statistical Program for the Social Sciences (SPSS) for further analysis.

iv) Physical measurements: Height, weight, body-fat percent, waist, hip, mid-arm circumference, biceps, triceps and subscapular skin folds will be measured by the RA with the participant wearing light clothing.

v) A 24-hour dietary recall will be completed by interview. Intake of total kilocalories, percentage kilocalories from protein, carbohydrate, total and saturated fat, lycopene, fatty acids, vitamin E and other vitamins will be calculated in grams for average 24-hour recall using the

Nutritionist VI software or the most recent update of this or a similar software. In addition to this single 24-hour dietary recall, study participants will be contacted on two other separate occasions (by telephone or mail) during the following 7 days to complete a second and third 24-hour dietary recalls, such that one of the recalls will be a week-end day.

vi) Fasting blood specimen collection:

Fasting venous blood, 30ml, will be collected with a multi-draw needle, into three separate tubes to provide serum and plasma for study biomarker analysis.

PSA: ToxMed laboratory, Nashville.

Vitamin E, androgens: Meharry Core laboratory.

IL-6, IGF & IGFBP-3: Meharry Core laboratory. (Future study)

8-isoprostane-PGF_{2α}: Jason Morrow's laboratory at VUMC.

Lycopene: Myron Gross's laboratory, University of Minnesota.

Fatty-acids: Kennedy Krieger Institute, Baltimore. Attention Ann Moser.

5-OHmdU: To be decided.

vii) Fasting Urine (10ml) will be collected and stored for future proteomics analysis as part of a pilot project that will be developed. Urine will only be collected from participants who consent to have their urine stored for such a future pilot study.

Follow-up Study visits at Time points at 3-, 6-, 12-month: (1hour)

i) Quality of Life (QOL) questionnaire will be self-administered, and complemented by interview as necessary.

ii) Physical measurements: Height, weight, body-fat percent, waist, hip, mid-arm circumference, biceps, triceps and subscapular skin folds will be measured by the RA with the participant wearing light clothing.

iii) A 24-hour dietary recall will be completed by interview. Intake of total kilocalories, percentage kilocalories from protein, carbohydrate, total and saturated fat, lycopene, fatty acids, vitamin E and other vitamins will be calculated in grams for average 24-hour recall using the Nutritionist VI software or the most recent update of this or a similar software. In addition to this single 24-hour dietary recall, study participants will be contacted on two other separate occasions (by telephone or mail) during the following 7 days to complete a second and third 24-hour dietary recalls, such that one of the recalls will be a week-end day.

iv) Fasting blood specimen collection:

Fasting venous blood, 30ml, will be collected with a multi-draw needle, into three separate tubes to provide serum and plasma for study biomarker analysis to be analyzed in the various laboratories as shown above.

v) Fasting Urine (10ml) will be collected and stored for future proteomics analysis as part of a pilot project that will be developed. Urine will only be collected from participants who consent to have their urine stored for such a future pilot study.

Labeling and storage of specimens:

All research blood and urine specimens will be stored in the PI's freezer located on the 3rd Floor of the West Basic Science Building at Meharry Medical College at -80°C until shipped on dry ice to the commercial, research and core laboratories for the various research related analysis of biomarkers and micronutrients. At the conclusion of the study, the rest of the samples will be stored for up to 20 years, or until completely used up, maintaining their identifiers in the case that future studies become funded to follow-up these participants. Thereafter utilized samples will be stored without any identifiers, and can then be used for other prostate cancer and related research. The

consent form that the participants will sign will provide an option for them to agree or not agree to have their samples stored and used for future research in this manner.

Labeling and storage of data:

Informed consent documents will be stored in a locked cabinet in the PI's office at Meharry Medical College. These forms will be destroyed by shredding 5 years after the completion of the study. All research records will also be stored in a locked cabinet in the PI's office at Meharry Medical College and will be shredded 5 years after the completion of the study. Research data will be entered and stored as electronic files in the PI's personal computer hard-drive, and will also be saved onto a jump-drive. The computer database that will be used for data analysis purposes will not contain any names. This file will be kept indefinitely, and will be made available to graduate students to use as part of their course exercise in data analysis. The electronic study file that contains names and study identification numbers will be deleted 20 years after the conclusion of the study. This file is being maintained to provide the opportunity to invite interested participants to consider participation in future studies to investigate aspects of disease progression yet to be determined, and to also allow for long-term follow-up studies.

h. Clinical Assessment

Baseline and follow-up evaluations will be conducted at the time-points shown below.

Laboratory & Other Measures	Data Collection Time Line				
	Baseline Studies	Follow-up Time-Points (Month)			
		3	6	9	12
Clinical Symptom/QOL Assessment	X	X	X	X	X
Body-fat measures	X	X	X	X	X
Dietary Assessment (BLOCK FFQ)	X				X
Three 24-Hour Dietary Recall	X	X	X	X	X
Lycopene & Vitamin E	X	X	X	X	X
8-isoprostane-PGF _{2α}	X	X	X	X	X
Serum PSA (Free & Total)	X	X	X	X	X
Fatty-acids	X		X		X
Testosterone (Free, Total, DHT)	X	X	X	X	X
Comprehensive Metabolic Panel (CMP)	X	X	X	X	X
X-rays and Scans (Abstracted from Medical Record)	X	As clinically available			

* Blood Samples will be stored for future studies to measure a biomarker of DNA damage, 5-OHmdU, a biomarker of inflammation, IL-6, an antioxidant, Tocopherols, and other biomarkers that may inform the mechanism by which lycopene impact PSA levels, Plasma IGF-1 & IGFBP-3.

Clinical evaluations will be specifically conducted at the frequency and time-point shown below.

Clinical & Follow-up Procedures	Data Collection Follow-up Time-Points: (Month)														
	Baseline Studies	Study Intervention Period										Post-Study			
		1	2	3	4	5	6	7	8	9	10	11	12	15	18
Clinical Symptoms	x	X		x			x			x			x	x	x
QOL Assessment	x	X		x			x			x			x	x	x
Adverse Events	N/A	4x	2x	x	x	x	x	x	x	x	x	x	x	x	x

There will be a total of 6 questionnaires and forms to be completed, and copies are attached.

- 1 Personal and medical history questionnaire
- 2 QOL assessment (FACT-P)
- 3 Block FFQ
- 4 Adverse event form
- 5 Laboratory analysis form
- 6 X-ray & Bone-Scan form

i. Research Interventions: (Provide a list in chronological order of all research interventions that the subject will experience.)

STUDY ARM	AGENT	DOSE,	ROUTE,	FREQUENCY	DURATION
ARM-A	Lycopene	30 mg,	PO,	Daily	12 months
ARM-B	Lyc-O-Mato® (Tomato-Extract)	30 mg,	PO,	Daily	12 months

Research interventions/procedures that participants will undergo include the following:

Initial visit:

- 1) Eligibility determination by interview, and signing a short consent to be contacted.
- 2) Demographic & medical Information

First study visit:

- 1) Informed Consent: Reading the consent document, or having it read to them, followed by questions and answers for clarification as needed. Then signing the consent form, and receiving a copy.
- 2) Completing baseline study questionnaires
- 3) Blood draw
- 4) Physical measurements
- 5) Providing urine sample

Four follow-up visits at 3 months intervals

- 6) Completing study questionnaires
- 7) Blood draw
- 8) Physical measurements
- 9) Providing urine sample

Telephone calls:

- 10) Appointment reminders for each visit
- 11) 24-hour dietary recall by telephone interview
- 12) Calls to monitor adverse events

Letters in the mail

- 13) Appointment reminders
- 14) 24-hour dietary recall to be completed if hard-copy is preferred over telephone interview.

j. Data Management and Analysis:

1) Overall approach to data management:

An electronic data collection program will be developed to include all study questionnaires, and this program will be utilized for all patient interviews. Information received from laboratories or abstracted from medical records will also be entered into this program. Collected data can be transferred to SPSS or SAS as required. Nutrient intake information obtained from the Block FFQ will be entered directly into the SPSS database. The PI/Investigators can carry out interim data analysis at any time-point. This data analysis performed by the statistician in SAS will be utilized in reporting the study findings.

2) Plan for real-time data transfer:

As stated above most of the study data will be collected in real-time, while information that become available weeks after the interview can then be entered at that time.

3) Statistical plan:

Sample size calculation:

The study sample size has been estimated at 78 men. With an alpha of 0.05, power set at of 80%, and a conservative PSA slope reduction of 30.0%, 39 participants are proposed for each study arm for a 12-month intervention period. With the anticipation of a 15% drop-out rate, we plan to enroll up to 90 study-eligible patients into the study. PSA reduction, 'PSA slope', is an accepted surrogate endpoint for screening new agents against prostate cancer. A dietary intervention for prostate cancer patients estimated a sample size of 30-40 patients based on a PSA slope reduction of 70%, and power of 80% (102, 103). An isoflavone intervention study for prostate cancer patients utilized a linear mixed effects modeling for repeated measures to calculate the required sample size, and were able to detect a PSA slope reduction from 31.0% pre-intervention to 9.0% post-intervention with a sample size of 17 (104).

Based on available preliminary data, significant changes in the biomarkers of interest can be anticipated during a 6-month intervention. However it is desirable to study nutrient effects over longer periods as will be the case in reality, thus warranting a one-year intervention. Using a two-sample t-test analysis for the difference between slopes, and with given significance level and power, the following sample sizes were estimated for different PSA reduction slopes.

Sample Size Calculation for a Two-Arm Intervention Study for Different PSA Slope Reductions

Significance Level	Slope Reduction (%)	Subjects Per Study-Arm	
		Power (80%)	Power (90%)
0.05	30	39	51
0.05	40	22	29
0.05	50	14	19
0.05	70	8	10

Since there can be increases as well as decreases in the means of all other study biomarker endpoints, changes can be detected even at 90% power, using a two-sided test at 0.05 significance level. Based on a sample size of 39 per group we will have 90% power to detect a mean difference of 0.26 $\mu\text{mol/l}$ plasma lycopene between the treatment groups (common standard error of 0.35

μmol/l), a difference of 4.9 pg/ml of F2-isoprostane between the groups (common standard deviation of 4.9 pg/ml), and a PSA difference of 2.45 ng/ml, after a 6-month intervention, assuming a common standard deviation of 3.3 ng/ml. Following out to 12 months will increase our likelihood of finding significant mean differences, even if the slope reduction remains constant over time. The PSA level at the 12-month time-point is likely to be different from the pre-intervention values, and is hypothesized to be low in study Arm-A (single nutrient lycopene), and even lower in study Arm-B (Lyc-O-Mato®), than at baseline and at the 6-month time-point.

Data analysis:

Comparative analysis of the baseline differences in PSA (total & free), micronutrients (lycopene, fatty-acids, biomarkers (8-isoprostane-PGF_{2α}, Total & Free testosterone, DHT), physical measurements, and micro-nutrient intake estimates from the BLOCK FFQ between men in Study Arm-A and Study Arm-B will be assessed by basic statistical tests such as independent sample t-test. Other characteristics like age at diagnosis, current age, PSA at diagnosis, Gleason score will also be compared by t-test to document comparability of both study arms at baseline. Correlation between the nutrients and the biomarkers will be assessed by Pearson's (skewed data) or Spearman's (normally distributed data) correlation, depending on the pattern of distribution, at baseline.

The effect of the interventions will be analyzed based on evaluable patients as well as by intent-to-treat. This trial is a 2-arm randomized study with the treatment arms being Lycopene capsule vs Lyc-O-Mato® capsule. The primary biomarker outcome measures are serum PSA (Free & Total) and 8-isoprostane-PGF_{2α}.

Three main methods will be utilized in this analysis:

iv) Changes in mean measures of biomarkers

Mean values for biomarkers will be compared across both study arms using Paired-sample t-test to compare the pre- and post-intervention effect of each treatment.

v) Changes in biomarker slope will be assessed in two ways:

- a) Comparing mean slope changes during intervention across study arms for PSA and other biomarkers.
- b) Comparing mean changes in slope between pre- and post-intervention PSA measures across study arms. (Multiple PSA measures are usually available for prostate cancer patients)

vi) Proportion of patients with appreciable PSA reduction (or other biomarker changes) will be compared across treatment group by Chi-Square test.

- a) Appreciable PSA and other biomarker reduction (or increase) will be set at 30%, 50% and 70%.
- b) Proportion comparison for those who had complete, partial, or no PSA response, or disease progression (increased PSA) between Study Arm-A and Study Arm-B will be by Chi-square test.

Response definitions:

-Complete PSA response (CR):

- i) Normalization of PSA to undetectable levels for 2 successive determinations at least 3 months apart among patients who had radical prostatectomy.
- ii) Normalization of PSA to nadir value sustained for 2 successive determinations at least 3 months apart among radiotherapy patients.

-Partial response (PR):

≥50% reduction from baseline PSA sustained for at least 2 successive determinations at least 3 months apart.

-Progressive disease (PD):

≥ 50% increase from baseline PSA, or the minimum PSA level observed during the study, sustained for two successive determinations at least 3 months apart.

-Stable disease (SD):

Does not qualify for CR, PR or PD, with PSA remaining as at the time of randomization.

iv) The main effect of lycopene intervention (PSA reduction), and the effect interaction with prostate cancer treatment, (radical prostatectomy or radiation), can be tested. If the interaction effect upon any of the primary endpoints is statistically significant, then a stratified analysis will be necessary, evaluating the effect of lycopene separately for each treatment stratum.

Methods to monitor quality and consistency of the intervention and data collection:

The consistency of the intervention will depend mainly on the pharmacist who is responsible for ensuring that the supplement dispensing containers are labeled accurately, and that the correct intervention is placed in the containers as coded. The pharmacist will work with an assistant such that between the two of them they will have checks and balances to ensure accuracy.

Data collection will be monitored for quality control and consistency in two ways: Firstly, data that is entered directly into the database in real-time by the RA will be monitored by direct observation by the nurse coordinator, the nurse coordinator acting as check for accuracy. The PI will randomly observe data collection at least once in a month for adherence to the protocol. Secondly, for data such as laboratory results, medical record abstracts, and x-ray and bone-scan information that will be manually entered into the database, the nurse coordinator will supervise such entries, and the PI will cross-check one in every seven entries for accuracy.

4) Data security measures:

Study data will be stored on the PI's lap top, desk top, and one flash drive. These files will be password protected and only the PI, nurse coordinator and RA will have password access to these files. Other investigators can have access to the data through the PI or nurse coordinator. For purposes of data analysis the statistician will receive an electronic data file for which she will provide a separate password. All hard copies of study related information will be stored in a locked cabinet in the PI's office.

k. Description of protocol Drugs or Devices

Nutritional supplements are not considered drugs, however the two supplements to be used in this proposal are:

Lycopene Supplement:

Capsules containing 30 mgs of lycopene will be constituted at the Meharry Pharmacy to look exactly like the Lyc-O-Mato capsules. The capsule case will be obtained from the LycoRed Natural Products Industries, Beer-Sheva, Israel, makers of the Lyc-O-Mato® capsules.

Tomato-Extract Supplement: Lyc-O-Mato®

The tomato-extract soft gel capsules (Lyc-O-Mato®, LycoRed Natural Products Industries, Beer-Sheva, Israel) contain 30mg of lycopene and some minor carotenoids, phytoene, phytofluene and natural tomato matrix and gelatin. There are no added chemicals or micronutrients. Lyc-O-Mato® is produced from specially bred and cultivated lycopene rich tomato varieties developed in Israel by the late Professor Rafael Frankel. These tomatoes contain 3 times greater lycopene than regular tomatoes. LycoRed's hybrid tomatoes were developed through conventional agro-breeding

techniques, without using genetic engineering methods. LycoRed's proprietary production process does not involve the use of chemicals, therefore possibility of chemical contaminants in the capsules has been eliminated. In addition to lycopene, very small quantities of other bioactive molecules are found in the Lyc-O-Mato® capsules. These include other natural constituents of tomatoes, such as tocopherols, phytosterols, beta-carotene, phytofluene, phytoene, and zeta-carotene. The capsules do not contain any additives, synthetic or natural.

- i. IND/IDE number and name of sponsor, if the study is in support of an application to the FDA.

N/A

- ii. Complete names and composition of all medication(s), device(s), or placebo(s).

Lycopene supplement

Lyc-O-Mato® tomato-extract supplement

- iii. Source of medications, devices, or placebos.

Lycopene supplement:

To be constituted at the Meharry Pharmacy to look exactly like the Lyc-O-Mato capsules. The capsule case will be obtained from the LycoRed Natural Products Industries, Beer-Sheva, Israel, makers of the Lyc-O-Mato® capsules.

Lyc-O-Mato® tomato-extract supplement:

The tomato-extract soft gel capsules (Lyc-O-Mato®): LycoRed Natural Products Industries, Beer-Sheva, Israel.

- iv. Location of storage for study medications.

Meharry Pharmacy

- v. Dose range, schedule, and administration of test articles.

30mgs, once daily, oral route.

- vi. Washout period, if used, should be described in detail.

N/A

- vii. Duration of drug or device treatment.

12 months.

- viii. Concomitant medications allowed.

Prescriptions, over the counter pain/sinus medication.

- ix. Antidotes and treatments available.

N/A

- x. Disposition of unused drug.

Unused supplement will be offered to faculty and staff at Meharry, and the rest will be disposed by the study pharmacist at Meharry Metro General Hospital.

- xi. The procedure by which the IND sponsor will monitor the protocol in accordance with 21 CFR 312.

N/A

- xii. The following items are attached:

(1) A copy of the Investigator's Brochure is attached. This is not an approved drug for a new indication, and the copy of the package insert is not attached.

(2) A signed Form FDA 1572 for IND Applications filed with the FDA, including the following information (for non-FDA new drug protocols, the following information should be included in the protocol):

N/A

(a) Name, address and a statement of the qualifications for each investigator and the name of each sub-investigator working under the PI.

Flora A. M. Ukoli, MBBS, DPH, MPH.

Department of Surgery, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd., Nashville, TN 37208.

Dr. Ukoli holds a medical degree, and two masters degree, one in public health and the other in epidemiology, not currently licensed to practice medicine in the United States, and an epidemiologist in the area of chronic diseases including cancers.

Ronald Davis, M.D.

Department of Surgery, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd., Nashville, TN 37208.

Dr. Davis holds a medical degree, and he is a licensed board certified practicing urologist.

Anthony Archibong, Ph.D.

Department of OB/GYN, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd. Nashville, TN. 37208.

Dr. Archibong holds a doctorate degree in biochemistry.

Emeka Ikpeazu, M.D., Ph.D.

Department of Medicine, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd. Nashville, TN. 37208.

Dr. Ikpeazu holds a doctoral degree in biomedical sciences, and a medical degree, and he is currently a licensed board certified practicing oncologist.

Derrick Beech, M.D.

Department of Surgery, Meharry Medical College, 1005 Dr. D. B. Todd, Jr. Blvd., Nashville, TN 37208.

Dr. Beech holds a medical degree, and he is a licensed board certified practicing general surgeon.

Jay H. Fowke, PhD.

Vanderbilt Epidemiology Center, Division of Internal Medicine and Public Health, 1215 21st Street South

Vanderbilt University Medical Center, 6110 Medical Center East, Nashville, TN 37232-8300

Dr. Jay Fowke holds a doctoral degree in epidemiology and a masters degree in neuroscience. He is a practicing epidemiologist in the area of cancer and nutrition.

Bonnie LaFleur, Ph.D.

Department of Biostatistics, Vanderbilt University Medical Center, 571 Preston Research Building, Nashville, TN 37232-6848.

Jason D. Morrow, M.D.

Division of Clinical Pharmacology, 536 Robinson Research Building 23rd Ave S @ Pierce, Nashville, TN. 37232-6602

Dr. Jason Morrow holds a medical degree, and is a licensed, board certified practicing physician, with an active research laboratory.

Michael Cookson, M.D.

Department of Urologic Surgery, Vanderbilt University Medical Center, A 1302 MCN, Nashville, TN 37233

Dr. Michael Cookson holds a medical degree, and he is a licensed, board certified practicing urologist.

Myron D. Gross, Ph.D.

University of Minnesota, Division of Epidemiology, 1300 South Second Street, Suite 300, Minneapolis, MN 55454

Dr. Myron Gross holds a doctoral degree in biochemistry, and runs an active research laboratory.

Omer Kucuk, MD., FACN.

Division of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University, 4100 John R, 4-HWCRC, Detroit, MI 48201

Dr. Omer Kucuk holds a medical degree and he is a licensed, board certified practicing oncologist, and runs an active research laboratory.

(b) Names and addresses of facilities to be used.

-Meharry Medical College, Nashville, Tennessee.

1005 Dr. D. B. Todd, Jr. Blvd., Nashville, TN 37208.

-Vanderbilt University Medical Center, 1215 21st Street South, Nashville, TN.

6110 Medical Center East, Nashville, TN 37232-8300

(c) Name and address of each IRB reviewing the protocol.

-Human Protections Administrator

Office of Grants Management, Meharry Medical College

1005 Dr. D. B. Todd, Jr. Blvd, Nashville, TN 37208. Telephone: 615-327-6703

-VU Institutional Review Board

504 Oxford House, Nashville TN 37232-4125. Telephone: 615-322-2918

Name of IRB of Record: Meharry Medical College (Meharry Med Coll)

(1) Assurance Type (HHS, DOD) and Number: FWA00003675

(2) Date of approval of IRB of Record: October 29, 2002 – August 17, 2008.

(3) Risk Level given to study by IRB of Record: In Review Process

(4) Date of next continuing review by IRB of Record: N/A at this time

Name of IRB of Record: Vanderbilt University

(1) Assurance Type (HHS, DOD) and Number: FWA00005756

(2) Date of approval of IRB of Record: March 5, 2004 – March 5, 2007.

(3) Risk Level given to study by IRB of Record: VU IRB will not receive application until approved by the MMC IRB

(4) Date of next continuing review by IRB of Record: N/A at this time.

(3) For Investigational Devices, include your local IRB's assessment of the risk (non-significant or significant) of the investigational device you plan to use in your study. If the device

poses significant risk to research subjects, specify the IDE number obtained from the FDA, the name of the sponsor, and the procedure by which the sponsor will monitor the protocol in accordance with 21 CFR 812.

N/A

1. Risks/Benefits Assessment:

i. Risks to Subjects.

Procedure	Risks	Measures to Minimize Risks
Fasting Blood Draw	Discomfort of skipping breakfast Pain from needle prick Slight bruising at needle site	Eat breakfast after blood draw if hungry. Reassure before sticking patients. Use 23 or 21 gauge butterfly needles. Trained and certified phlebotomist will draw the blood.
Urine collection	There are no known risks of collecting urine sample.	Adequate counseling and instruction about the procedure to collect urine sample.
Intervention (Lycopene) for 12 months	Commonly used nutrient supplement with no known risk. Mild diarrhea has been reported in one study participant.	Patients will be educated to report any adverse effect to the study coordinator & PI immediately, and to stop taking supplement until they are reviewed by their physician. A schedule to regularly call participants to monitor adverse events is in place through out the intervention. An adverse event management procedure will be put in place to protect affected participants, and to halt the study if the intervention is deemed unsafe.
Collection of personal & Medical information	Breach of confidentiality	Participants will be assigned a study identification number. Their names will not be listed on the research database. A register of names and identification numbers will be kept in a separate file by the PI. All research staff will be trained to adequately handle patient information from their medical records or research records in complete confidence.

ii. Benefits to Subjects.

The direct benefit to study participants is the possibility of reducing the rate of cancer progression expected from the cancer inhibiting antioxidant effect of lycopene both in the form of a single nutrient or whole-food supplement. The study outcome regarding the role of lycopene in prostate carcinogenesis will inform nutrient supplement education for current and future patients, even in the absence of direct benefit to the participants. The participants will have the satisfaction that the results of the study will provide needed information about the usefulness of dietary lycopene in prostate cancer risk control, and that such information will be utilized in developing appropriate

nutrition education, and nutrient supplement recommendations for the control of prostate cancer progression. Such information may also be useful in developing education material for prostate cancer prevention especially among African-American men in particular. A negative finding will be beneficial as it will provide the platform to advise patients such that they do not spend unnecessary expense on such supplements for cure.

It has been our experience that many men worry about the health effects of the foods they eat, the supplements they take, and the supplements they are not taking. By participating in this study the patients will have a chance to talk about, and gain some insight into their dietary pattern, receive contact information about the nutrition unit at Meharry if requested, and at least they will be assured that they are proactively addressing their prostate health.

iii. Payment of study incentive to participants.

Participants will receive a total of \$140.00, \$120.00 in cash and gifts worth \$20, only if they complete the study. The cash incentive is provided towards the cost of transportation and parking, and the inconvenience of the blood draw, while the study promotional 'Thank-you' gifts are presented in appreciation of their time and commitment to the completion of the study. Compensation for participating will be prorated as follows:

Cash incentive:

Initial visit:	\$10
1 st Study visit:	\$30
(Blood draw, other questionnaires, and BLOCK FFQ)	
Follow-up visits (4 time-points) @ \$20	\$80
3-, 6-, 9-, 12-month	
(Blood draw, other questionnaires, and FFQ-T)	

Gift incentive:

T-Shirt:	Recruitment	(\$10.00)	\$20
Mug:	6-month	(5.00)	
Certificate/Pin:	End of intervention	(5.00)	

m. Reporting Serious or Unexpected Adverse Events

i. Serious or unexpected adverse events can occur in any and all types of studies, not just experimental interventions or clinical trials.

ii. Definition of Adverse Event in this proposed study:

1) An adverse event will include any illness (vomiting, diarrhea, severe pain), or feeling of discomfort experienced by the participant. This definition includes inter-current illnesses and injuries, and exacerbations of preexisting conditions. Death from any cause is also an adverse event. (Definitions as described in 21 CFR 312.32)

2) An adverse event temporally related to participation in the study will be documented whether or not considered to be related to the test article. This definition includes inter-current illnesses and injuries, and exacerbations of preexisting conditions. The following information will be included in the report of the event: Subject identification number and initials; associate investigator's name and name of MTF; subject's date of birth, gender, and ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route and duration of treatment, and date of last dose. (Adverse effect form attached)

Potential adverse effects will be monitored, recorded and reported according to NCI guidelines using the NCI Common Toxicity Criteria Version 2. These nutritional supplements have not been reported to have any side effects in previous short duration studies. In a one-year

intervention study only one of 36 patients reported diarrhea (grade 2 toxicity) as a result of the supplementation with lycopene using a dose range from 15mgs daily to 120mgs daily. We do not expect significant toxicity in this study that plans to supplement a daily dose of 30 mg of lycopene for 12 months. It is noted that 30mgs lycopene is present in 1 cup of tomato sauce, the equivalent of 2 servings of tomato sauce. In certain Mediterranean countries it is usual to consume more than a cup of tomato sauce frequently without any side effects. If moderate to severe supplement related adverse effects are reported or observed by the participant, that participant will stop taking the supplement immediately until a decision to continue or withdrawn from the study is received from the Meharry IRB.

Adverse effects will be monitored by calling participants weekly in the first month, every other week in the second and third months and monthly thereafter. Participants will be instructed to call the study number if they experience any effects they attribute to the supplementation. They will also be reminded to call the usual emergency number for all other emergencies. We plan to have access to information collected during their regular medical examination as scheduled by their urologist. In addition the study will monitor the health of participants using a quality of life (QOL) assessment tool, physical measurements of body fat distribution, and a comprehensive metabolic panel laboratory test. This assessment will be conducted at baseline and quarterly throughout the study duration. Information about their x-rays and scans will be abstracted from their medical records. This way any adverse changes in the patients' health will be noticed, and immediately conveyed to their physician for appropriate measures. If these adverse changes are thought to be related to the study intervention, the patient will be immediately withdrawn from the study. (See adverse event flowchart)

All adverse events will be reported immediately, on the Meharry Adverse Events Form, to the Clinical Trial Office, the Medical Monitor, Alphonse Pasipanodya, M.D., the Meharry Medical College IRB, and the participants urologist/oncologist. The IRB and the Medical Monitor will then fully discuss the situation and make a decision within 72 hours either to amend the protocol for dose modification, withdraw the affected individual from the study, or halt the entire study. Their decision will then be communicated to the PI for immediate implementation. For participants with moderate to severe adverse reactions to supplementation, a dose modification to 15mgs lycopene per day will be tried for tolerance before deciding to withdraw the patient completely. Adverse events will be treated as usual emergency care at presentation. Participants who present to Meharry will be assessed and managed by the medical monitor, Alphonse Pasipanodya, M.D., at no cost to the study participant.

All unexpected or fatal toxicities (including suspected reactions) will be reported to the Clinical Trials Office, the Medical Monitor, and the Meharry IRB, and the HSRRB of the Department of Defense

- iii. Point of Contact information of agencies or offices to be notified in the event of a serious and unexpected adverse event:

Internal:

- i) Flora A. Ukoli (PI) at 615-327-5653 or Research assistant at 615-327-5668.
- ii) Saundra Motley, VU nurse/coordinator, at 615-936-3418
- iii) Lavenia Crutcher, MMC nurse/coordinator, at 615-327-5651
- iv) Alphonse Pasipanodya, M.D. Medical Monitor, at 615-327-6555
- v) Chair of the Meharry Institutional Review Board James Potts, M.D. at 615-327-2992
- vi) Office of the Human Protections Administrator, Cynthia Weaver, at 615-327-6703.

External:

Adverse experiences that are both serious and unexpected, unanticipated problems involving risk to volunteers or others, and all volunteer deaths will be immediately reported by telephone to the USAMRMC Deputy Chief of Staff for Regulatory Compliance and Quality at 301-619-2165, and by email to hsrrb@det.amedd.army.mil, or by facsimile to 301-619-7803 to the U.S. Army Medical Research and Materiel Command's Human Subjects Review Board (HSRRB). A complete written report will follow the initial telephone call within 3 working days. In addition to the above, a complete written will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

The Medical Monitor:

The medical monitor will review all unanticipated problems, serious and unexpected adverse events involving risk to the study volunteers and others, and all volunteer deaths associated with the protocol and provide an unbiased written report of the event within 10 calendar days of the initial report. At a minimum, the medical monitor will comment on the outcomes of the adverse event or problem and in the case of a serious adverse event or death comment on the relationship to the participation in the study. The medical monitor will whether he/she concurs with the details of the report provided by the study investigator, PI. The medical monitor will forward reports to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012. Reports of events determined by either the PI or Medical Monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the HSRRB by facsimile to 301-619-7803.

n. Disposition of Data

All study related documents such as informed consent documents, completed questionnaires, laboratory reports will be destroyed by shredding 5 years after the completion of the study. Research data stripped of identifiers stored in electronic files will be kept indefinitely, and will be made available to graduate students to use as part of their course exercise in data analysis. The electronic study register that contains names and study identification numbers will be deleted 20 years after the conclusion of the study.

o. Modifications to the protocol.

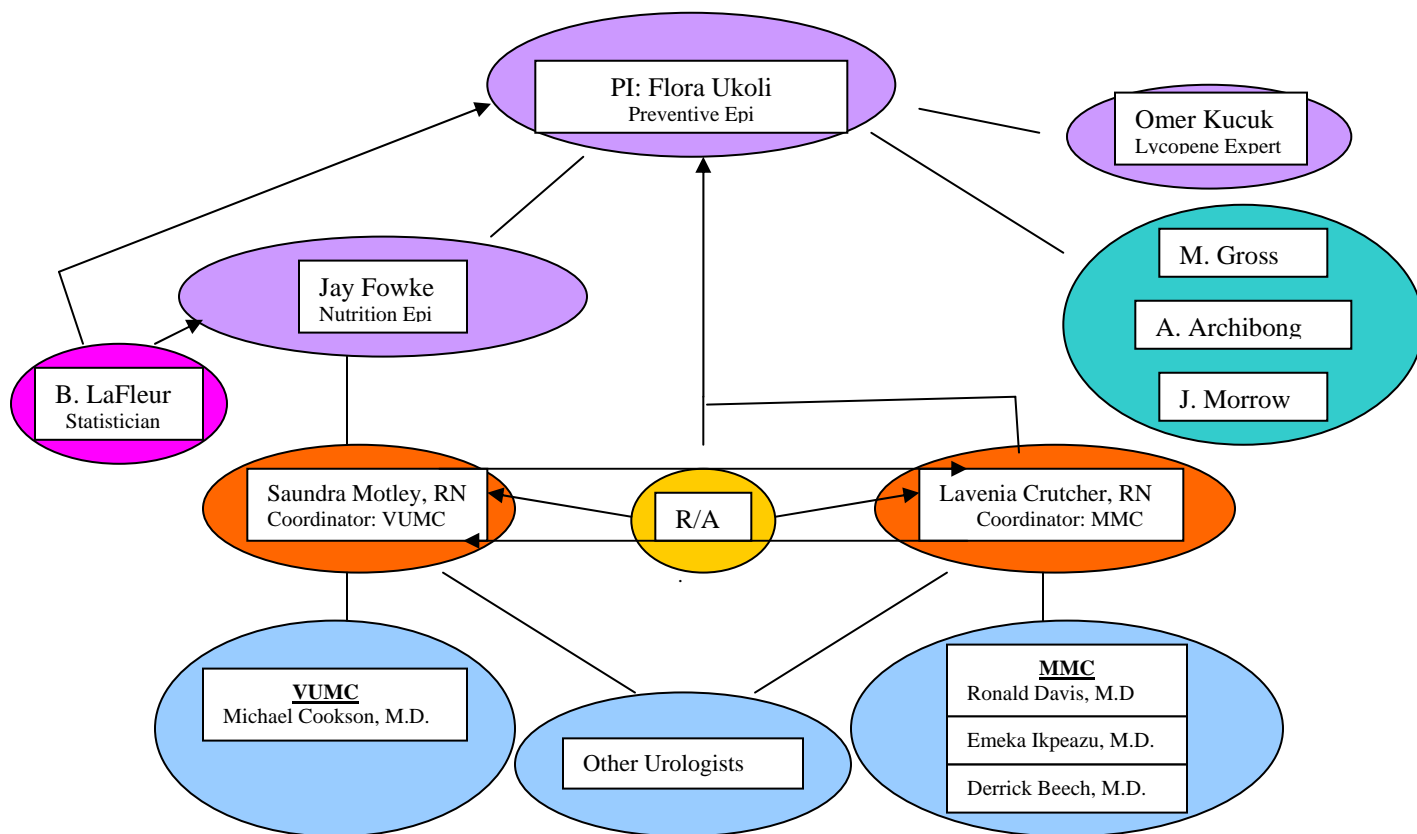
Any modification in the protocol that will involve participant recruitment, procedures, data collection etc. will be sent through the Meharry Medical College IRB, VUMC IRB, and the HSRRB for approval. The changes will not be effected until both approvals are received.

p. Departure from the protocol.

Any departure from the protocol will be reported to the Meharry Medical College IRB by telephone within 24 hours and in writing by email and/or letter within 72 hours by the PI. The PI will also notify the HSRRB within 72 hours, and will include the actions taken by the local IRB to address the departure from protocol.

q. Study Organization and Management Plan:

ORGANIZATIONAL CHART



PROGRAM TIMETABLE

TASKS	Program Period											
	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Start-Up, IRB, Purchase Supplies	X	X										
Recruit, Consent, Run-In trial	X	X	X	X	X	X						
Intervention and Data Collection			X	X	X	X	X	X				
Data Management		X	X	X	X	X	X	X	X	X		
Laboratory Assays					X	X	X	X	X			
Block FFQ Analysis							X		X			
Statistical Analyses						X	X	X	X	X		
Manuscripts and grant writing								X	X	X	X	X

23. **Volunteer Registry Data Base Requirement:** (Required for all greater than minimal risk **intramural** studies, studies conducted in USAMRMC laboratories or conducted by USAMRMC personnel, or in extramural studies if deemed necessary by the HSRRB. In addition, include the completion of the data sheets in the study procedure timelines. **If necessary, read, but do not remove the following paragraph which must also be included in the informed consent form.**)

It is the policy of the U.S. Army Medical Research and Materiel Command that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Data Base. The information to be entered into this confidential data base includes your name, address, Social Security number, study name and dates. The intent of the data base is two-fold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years.

Upon the completion on the study, the data sheets will be sent to the following address:

Commanding General, U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
504 Scott Street
Fort Detrick, Maryland 21702-5012

24. The PI will submit continuing review reports and a final study report to the HSRRB for acceptance.

25. Representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research.

References:

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Appendix 13

Seminar schedule

Speaker: Ram Dasari, M.D. (Urologist)

Urology Associates, Nashville.

Title of presentation: “PSA Failure after local treatment of prostate cancer: What next?”

Date: Friday February 16th, 2007 at 12:00 noon

Speaker: Omer Kucuk, M.D. (Oncologist)

Wayne State University, Detroit.

Title of presentation: “Lycopene in the etiology and control of prostate cancer progression”.

Date: Monday March 5th, 2007 at 12:00noon.

Speaker: Harvey Murff, M.D., MPH.

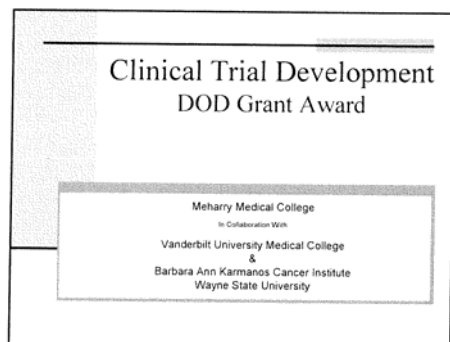
Vanderbilt University, Nashville.

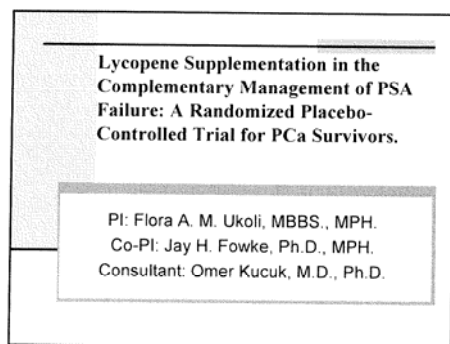
Assistant Professor, Internal Medicine, and IRB Committee member

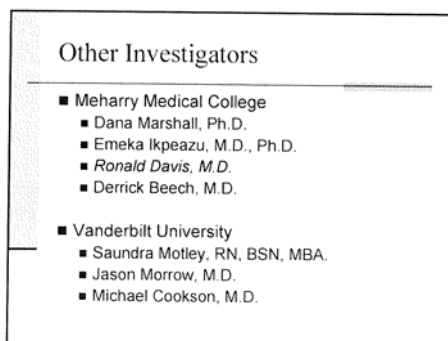
Title of Presentation: “Data Safety and Monitoring in Clinical Research”.

Date: Monday March 26th, 2007.

Appendix 14 “The role of lycopene in biochemical failure among prostate cancer survivors.”
Presented by Flora A. M. Ukoli. August 2006.







Background

- Incidence & mortality racial disparity due to several factors including genes & environment
 - Dietary risk & protective factors of PCa identified
 - Laboratory, animal & epidemiological studies
 - Lycopene (tomato-based antioxidant) is protective
- Lycopene intervention studies in humans
 - 3-week intervention: Pre-radical prostatectomy
- Dietary intervention / prevention strategy can focus on
 - Normal men
 - High risk men (Family hx, High-normal PSA, -ve biopsy)
 - Relapsing PCa survivors (Biochemical failure) *

Objectives

- Evaluate the feasibility and adherence to lycopene supplementation among Africa-American men with biochemical failure following PCa treatment.
- Determine if lycopene or tomato-extract supplements will better impact plasma lycopene.
- Assess if lycopene and/or tomato extract will decrease serum PSA in treated PCa patients presenting with biochemical failure.
- Assess the modulation of biomarkers of oxidative stress (isoprostane), inflammation (IL-6), and cell growth by lycopene.

Eligibility Criteria

- Ethnicity: African-American.
- Diagnosis: Histologically confirmed prostate cancer, treated by radical prostatectomy or radiation, seed implantation or external beam radiation.
- Presentation: Biochemical or PSA failure or relapse.
 - Defined according to treatment received:
 - Men who had radical prostatectomy:
 - Two successive readings, at least one month apart, of PSA ≥ 0.4 ng/ml, after initial fall to undetectable level
 - Men who had radiation treatment:
 - Two successive readings, at least one month apart, of PSA above the lowest value attained (nadir) after radiation.
- Consent: Must sign informed consent.

Exclusion Criteria

- Enrolled in diet related trial with overlapping intervention/follow-up period.
- Taking supplements that are known to contain lycopene, or any micronutrient supplements other than multivitamins.
- Life-expectancy less than 1 year by clinician recommendation.
- Mental incompetence
- Erratic life-style, have 5 or more alcoholic drinks/day
- Extensive travel or institutionalized and cannot keep follow-up appointment.
- Organ function restrictions.
- Chemotherapy within 4 weeks of starting intervention
- Hormonal therapy within 4 weeks of starting the intervention
- Eligible for a higher priority study.

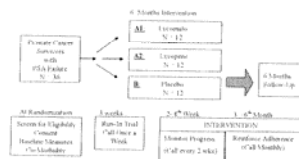
Method: Phase II CT

- Supplement Intervention Trial
 - Double-Blind
 - Randomized
 - Placebo-Controlled
- 3-Arm Study
- 6-Month Intervention
- Initial Follow-Up for 6 months
- Subsequent Follow-Up for up to 12 months

Treatment Plan

- **Arm A1: Tomato-Extract (Lyc-O-Mato ©) Supplement**
 - 30mgs lycopene on alternate days for 4 weeks, then daily
- **Arm A2: Lycopene Supplement**
 - 30mgs lycopene on alternate days for 4 weeks, then daily
- **Arm B: Placebo / Usual Care**
 - A placebo tablet (cellulose matrix identical to Lyc-O-Mato © on alternate days for 4 weeks, then daily
- All groups will continue
 - With their usual treatment
 - To eat their usual diet.

Randomization Plan



Data Collection Plan

Laboratory & Other Measures	Data Collection Time Line				
	Baseline Studies	Month-3	Month-6	Month-9	Month-12
Clinical Symptom Assessment	X	X			X
Body-fat measures	X		X		X
Dietary Assessment (FFQ)	X		X		X
Lycopodium	X	X	X	X	X
Isoprenoids & H ₂ O ₂ *	X	X	X	X	X
Serum PSA level	X	X	X	X	X
Triphosphoric fatty acids	X		X		X
Testosterone (Total and DHE)	X		X		X
Plasma HIF-1 and HIF1P-3	X		X		X
CBC with differential	X		X		X
SMA-12, Electrolytes	X		X		X
X-rays and Scans	X	Repeat as clinically indicated			X

Planning & Implementing CT

- Task 1 (Completed by the PI)
 - Submitted proposal in 2004 to conduct a dietary intervention. Good score, not refunded
 - Submitted a CT development proposal in 2005, and it was funded.
- Task 2 (This is where we are)
 - Develop the CT protocol, obtain IRB approvals
 - Identify other recruitment centers & other collaborators
 - Submit a full CT proposal to DOD or any other agency
- Task 3 (Once we get funded)
 - Conduct the CT

Commitment & Responsibilities

- Describe your role in this grant
 - ½ -page justification
- Protocol Development
 - Identify the portion of CT protocol to write
 - Submit written section within 3 weeks
- Submit any suggestions and comments to PI
- Introduce appropriate personnel to PI
 - Statistician
 - Pharmacist

Budget Plan

- The 1-year CT Development Grant
 - \$100,000 Funded
 - DOD will pay ½ now, ½ at conclusion
 - VU & Consultant will get only ½ budget up front
- The 3-year CT Grant to be Submitted
 - Revise the old budget
 - Appropriate % Effort for all investigators
 - Project staff: Saundra from VU & Miriam from MMC
 - Pharmacist: Service charge
 - Laboratory analysis (Extensive)
 - Supplies and Travel

SUPPORTING DATA: All figures and/or tables shall include legends and be clearly marked with figure/table numbers.